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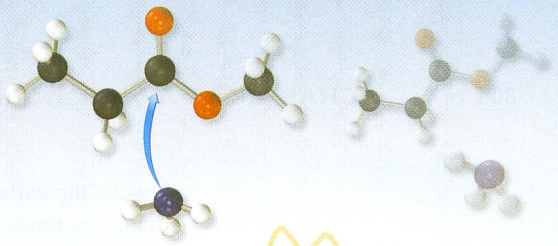

Substitutions at the Carbonyl Group

REACTIONS OF CARBOXYLIC ACIDS AND DERIVATIVES

CHAPTER 19

MASTERING ORGANIC CHEMISTRY

- Predicting the Products of Nucleophilic Substitutions at Carbonyl Groups
- Understanding the Mechanisms for These Reactions
- Predicting the Effect of the Structure of the Reactant on the Position of the Equilibrium for These Reactions
- Using These Reactions to Interconvert Any of the Carboxylic Acid Derivatives and to Prepare Aldehydes, Ketones, Alcohols, and Amines
- Using These Reactions to Synthesize Compounds

THE PREVIOUS CHAPTER discussed the attack of nucleophiles at the electrophilic carbonyl carbon of aldehydes and ketones. In most of the reactions this resulted in the addition of the nucleophile to the carbon and a proton to the oxygen of the carbonyl group. In this chapter the electrophile is the carbonyl carbon of a carboxylic acid or a related derivative such as an acyl chloride, anhydride, ester, or amide. The reactions in this chapter begin in exactly the same way as those in the last chapter—that is, by attack of a nucleophile at the carbonyl carbon. Here, however, the presence of the other heteroatom (an atom other than carbon or hydrogen, such as oxygen, nitrogen, or chlorine) on the carbonyl carbon causes the reaction to diverge at this point. Rather than the addition reactions of Chapter 18, the heteroatom group leaves, resulting in a substitution.

First, the general mechanisms for these reactions are presented. Then the reactivity of these carboxylic acid derivatives is discussed. As expected, the factors that control the reactivity are very similar to those that affect the addition reactions of Chapter 18. Next, reactions with nucleophiles that interconvert all of the members of the carboxylic acid family are presented. Finally, the reactions of hydride and organometallic nucleophiles with these electrophiles are discussed.

19.1 THE GENERAL MECHANISM

As was the case for nucleophilic additions to aldehydes and ketones, two mechanisms occur for the reactions in this chapter: one under basic conditions and one under acidic conditions. Both of these start in the same manner as the addition reaction mechanisms. The basic conditions mechanism is shown in Figure 19.1. First the nucleophile

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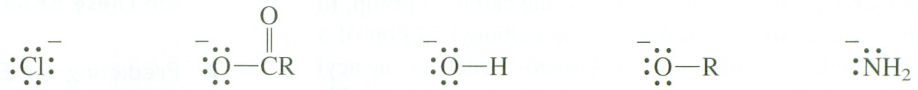
attacks the carbonyl carbon, generating an intermediate that is very similar to that produced by nucleophilic attack on an aldehyde or ketone. The major difference between this intermediate and that produced from an aldehyde or ketone is the ability of L to act as a leaving group in this case. In the second step, L leaves in a reaction that looks very much like the reverse of the first step. The overall result is a substitution of the nucleophile for the leaving group. Although this reaction is a substitution, it is important to note that the mechanism is quite different from the S_N2 mechanism that occurs at sp^3-hybridized carbons. This mechanism occurs in two steps, with the nucleophile bonding to the carbon first. Such a mechanism is impossible at an sp^3-hybridized carbon because the intermediate would have five bonds to the carbon and would violate the octet rule. At a carbonyl carbon a pair of electrons can be displaced onto the oxygen when the nucleophile bonds, resulting in the formation of an sp^3-hybridized carbon in the intermediate (often called the **tetrahedral intermediate** because of its geometry).

For this mechanism to occur for an aldehyde or ketone, hydride ion or a carbanion would have to act as the leaving group. These species are much too basic to leave under normal circumstances. In the case of carboxylic acid derivatives the leaving group is one of the following less basic species:



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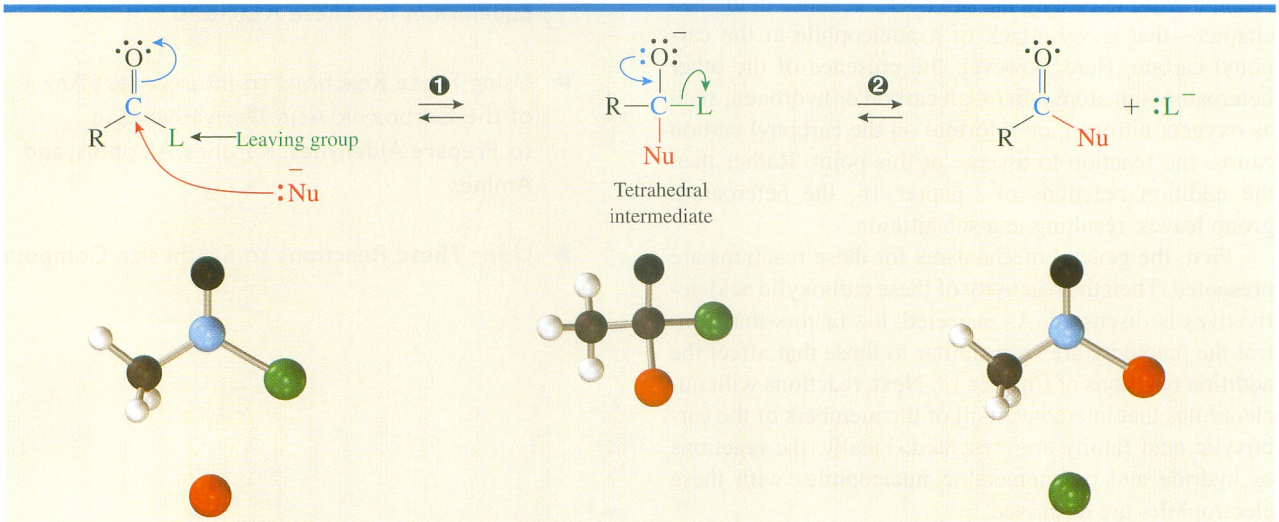
Click *Mechanisms in Motion* to view the **Mechanism of Nucleophilic Substitution at a Carbonyl Group under Basic Conditions.**



❶ The first step of this mechanism is exactly the same as the first step for nucleophilic addition to aldehydes and ketones under basic conditions (see Figure 18.1). The nucleophile may be uncharged in some cases.

This mechanism is sometimes called the **tetrahedral mechanism** because of this sp^3-hybridized intermediate with tetrahedral geometry. If L is H or R, it is too basic to leave as an anion, so aldehydes and ketones stop at this point. When L is Cl or an N or O group, it can better support a negative charge and is capable of acting as a leaving group.

❷ The overall result is a substitution of Nu for L. L^- must be a better leaving group (less basic) than H^- or R_3C^-.

Figure 19.1

MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT A CARBONYL GROUP UNDER BASIC CONDITIONS.

Except for chloride anion, these anions are too basic to act as leaving groups in the S_N2 reaction. However, poorer leaving groups can be used in this reaction because the first step, attack of the nucleophile, is usually the rate-determining step. The leaving group is lost in the subsequent step, which is favored by entropy because it is intramolecular.

As was the case for the addition reaction of Chapter 18, another version of the mechanism operates under acidic conditions. In this version the carbonyl oxygen is protonated before the nucleophile attacks. Because this makes the carbonyl carbon more electrophilic, weaker nucleophiles can be used (often the conjugate acids of those used under basic conditions). In addition, the leaving group may be protonated before it leaves. Examples of the acidic conditions mechanism are provided in later sections.

Now let's address the reactivity of these compounds—that is, how the rate and the position of the equilibrium for the reaction are affected by the structure of the compound. The first step, attack of the nucleophile, is usually the rate-determining step. Because this step is the same as the first step in the mechanism for additions to aldehydes and ketones, steric, resonance, and inductive effects control the rate of this reaction in exactly the same manner as was described in Sections 18.3 and 18.4. These effects can be summarized as follows:

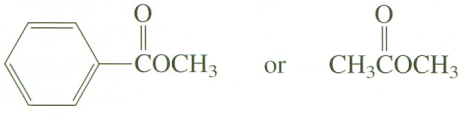
Steric effects: Steric hindrance slows the approach of the nucleophile and causes a decrease in the reaction rate. (However, the position of the equilibrium is not affected if the starting material and the substitution product have similar steric interactions.)

Inductive effects: Electron-withdrawing groups make the carbonyl carbon more electrophilic and increase the reaction rate; electron-donating groups make the carbonyl carbon less electrophilic and decrease the reaction rate.

Resonance effects: Resonance electron-withdrawing groups make the carbonyl carbon more electrophilic and increase the rate; resonance electron donors make the carbonyl carbon less electrophilic and decrease the reaction rate.

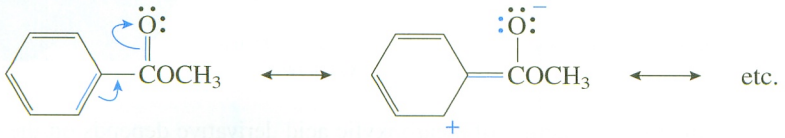
PRACTICE PROBLEM 19.1

Explain which of these compounds would have the faster rate of nucleophilic substitution at its carbonyl group:



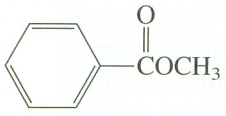
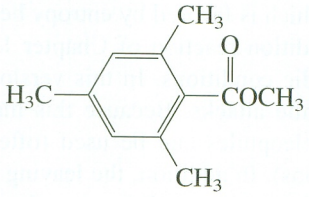
Solution

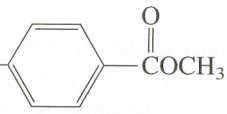
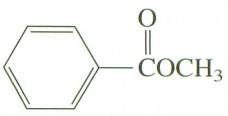
The benzene ring donates electrons to the carbonyl carbon by resonance, thus making the carbon less electrophilic and slowing the reaction rate:



PROBLEM 19.1

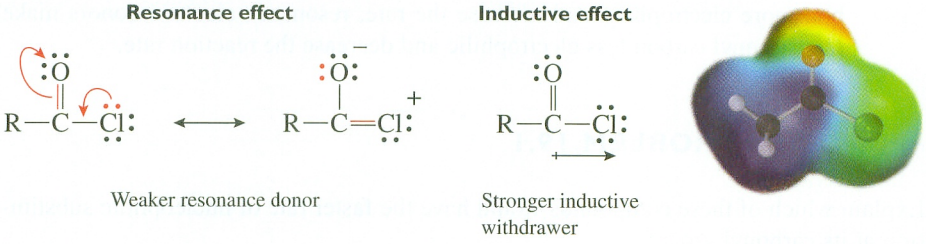
Explain which compound would have the faster rate of nucleophilic substitution at its carbonyl group:

a)  or 

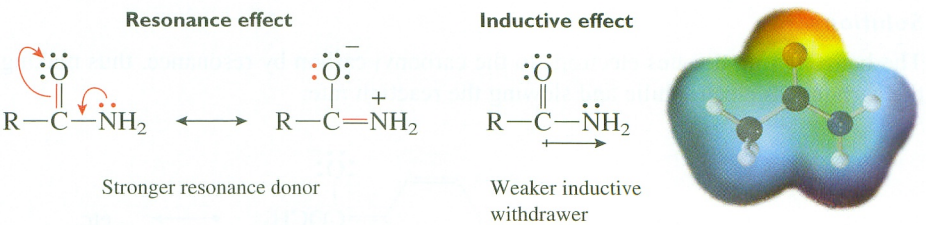
b) CF_3CCl or CH_3CCl c)  or 

Although the leaving group does not come off during the rate-determining step, it does affect the reaction rate by its inductive and resonance effects. Furthermore, its stability after it has left affects the position of the equilibrium. Leaving groups that are weaker bases are more stable and cause the products to be more favored at equilibrium.

Consider the case of an acyl chloride. The chlorine is an inductive electron withdrawer and a resonance electron donor. As we saw in Chapter 17, the inductive effect is stronger. (Recall that chlorine is not a very strong resonance electron donor because the long C—Cl bond and the size difference between the 3*p* AO on the Cl and the 2*p* AO on the C result in poor overlap of these orbitals.) In addition, chloride anion is a very weak base. Overall, acyl chlorides are the most reactive of the carboxylic acid derivatives discussed here and are the least favored at equilibrium.



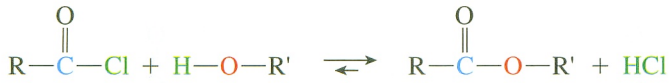
Now consider the case of an amide. The same effects are operating. The nitrogen is an inductive electron withdrawer and a resonance electron donor. As we saw in Chapter 17, the resonance effect is stronger in this case. Also, amide ion is quite basic. Overall, amides are much less reactive than acyl halides and are much more favored at equilibrium.



Although the rate of reaction of a carboxylic acid derivative depends on the inductive and resonance effects of the leaving group and the position of the equilibrium de-

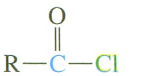
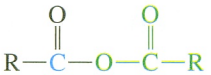
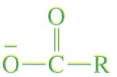
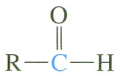
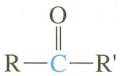
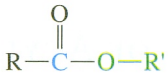
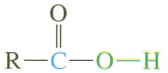
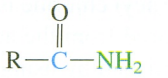
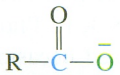
pends on the stability of the leaving group, both of these effects are related to the basicity of the leaving group. Acid derivatives with leaving groups that are weaker bases react faster and are less favored at equilibrium. Table 19.1 lists the reactivity order for all of these compounds. Note that aldehydes and ketones have been included in this reactivity scale, but for the rate of nucleophilic attack only. The second step, in which the leaving group comes off, does not occur for these compounds.

The reactivity scale of Table 19.1 is very important. Not only does it tell where a nucleophile will react when faced with a choice between two different carbonyl groups, but it also enables the position of the equilibrium to be predicted for many reactions. For example, a compound that has both an aldehyde and an ester group is more likely to be attacked by a nucleophile at the aldehyde carbonyl carbon. The table also indicates that the equilibrium in the reaction



favors the products because the ester is lower on the reactivity scale than is the acyl chloride. Any carboxylic acid derivative can readily be prepared by reaction of the appropriate nucleophile with a derivative that is higher on the scale. For example, an ester is often prepared by reaction of an acyl chloride with an alcohol, as shown in the preceding equation. Let's examine the details of how to prepare acid derivatives.

Table 19.1 Reactivity Scale for Carbonyl Compounds

Compound	Structure	Leaving Group	Comment
Most reactive compound			Less favored at equilibrium
Acyl chloride			
Anhydride			
Aldehyde			First step only
Ketone			First step only
Increasing reaction rate			Increasing equilibrium constant
Ester			Esters and acids are very similar in both rate and equilibrium position
Acid			
Amide			
Least reactive compound			More favored at equilibrium
Carboxylate anion		O^{2-}	Poor leaving group; seldom leaves

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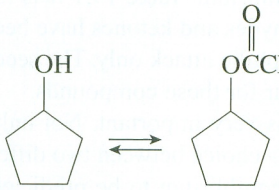
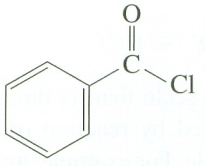
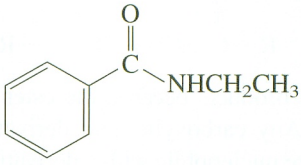
Click *Coached Tutorial Problems* for more practice using Table 19.1 to predict the position of the **Equilibrium in Carbonyl Group Substitutions.**

PROBLEM 19.2

Explain whether these equilibria favor the reactants or the products:

a) CH_3COCCH_3 +  + CH_3COH

b) $CH_3CH_2CNH_2 + CH_3OH \rightleftharpoons CH_3CH_2COCH_3 + NH_3$

c)  + $CH_3CH_2NH_2$ ⇌  + HCl

PROBLEM 19.3

Explain which of these reactions is faster:

$$CH_3COCH_3 + {}^-OH \longrightarrow CH_3CO^- + CH_3OH$$

or

$$CH_3CNHCH_3 + {}^-OH \longrightarrow CH_3CO^- + CH_3NH_2$$

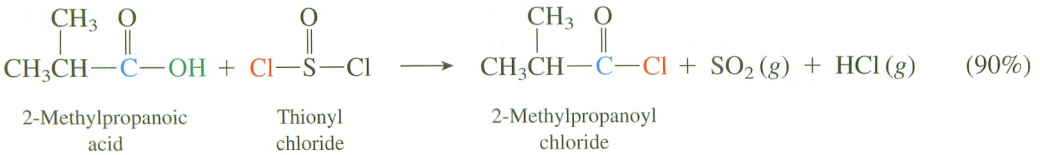
PROBLEM 19.4

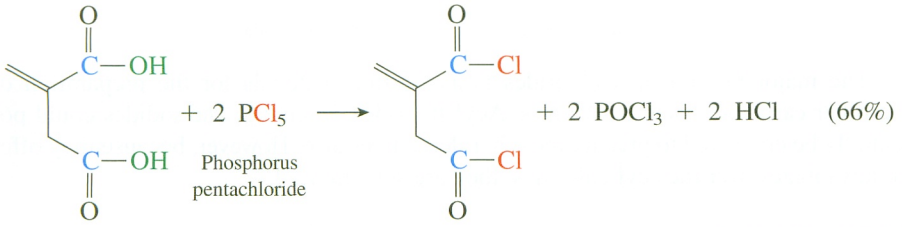
Suggest a reaction that could be used to prepare this amide:

$$CH_3CH_2CH_2CNHCH_2CH_2CH_3$$

19.2 Preparation of Acyl Chlorides

Because they are readily available from a number of synthetic reactions, carboxylic acids are the most common starting materials for the preparation of the other members of this family. Conversion of a carboxylic acid to an acyl chloride provides access to any of the other derivatives because the acyl chloride is at the top of the reactivity scale. But how can the acyl chloride be prepared from the acid when the acid is lower on the reactivity scale? This can be accomplished by using an even more reactive compound to drive the equilibrium in the desired direction. The reagent that is employed in the vast majority of cases is thionyl chloride, $SOCl_2$. Phosphorus trichloride, PCl_3, and phosphorus pentachloride, PCl_5, are also used occasionally. Examples are provided in the following equations:





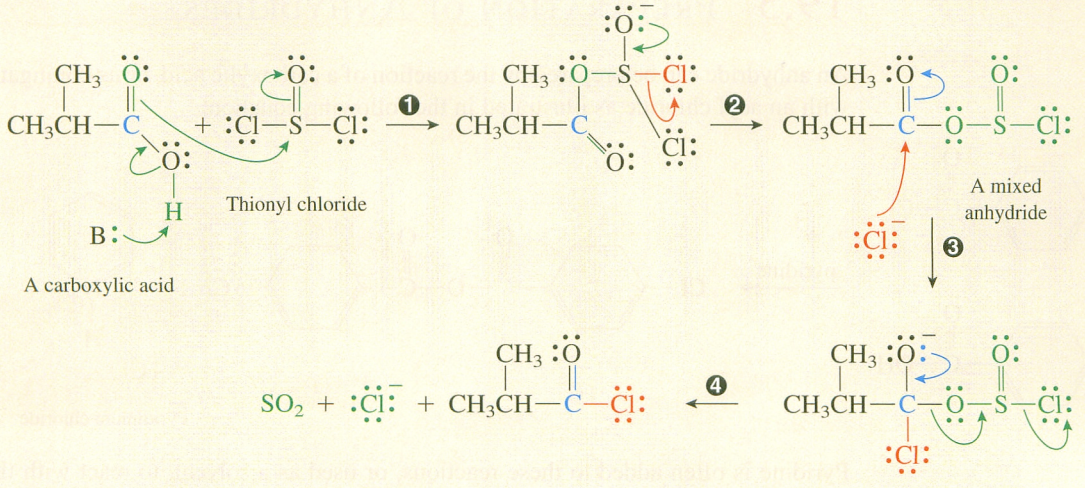
Thionyl chloride can be viewed as the di(acid chloride) of sulfurous acid. It is even more reactive than the acyl halide. Its reactivity, along with the formation of gaseous products (SO_2 and HCl), serves to drive the equilibrium to the acyl chloride. The mechanism for this reaction is shown in Figure 19.2. It is interesting to note that thionyl chlo-

❶ Thionyl chloride reacts like an acyl chloride. In this step, its sulfur–oxygen double bond plays the role of the carbonyl group of an acyl chloride. The nucleophile, the oxygen of the carboxylic acid, attacks the sulfur and displaces the pi electrons onto the oxygen.

❷ The reaction continues like the mechanism in Figure 19.1, but at sulfur rather than carbon. The electrons on the oxygen help displace the chloride.

This compound is a mixed anhydride of the carboxylic acid and sulfurous acid and is more reactive than the acyl chloride.

❸ The nucleophilic chloride anion bonds to the carbon, displacing the pi electrons onto the oxygen.

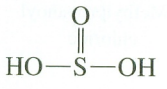


❹ The electrons on the oxygen help displace the leaving group, which fragments to SO_2 and Cl^-.

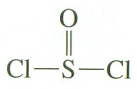
Figure 19.2

MECHANISM OF THE REACTION OF A CARBOXYLIC ACID WITH THIONYL CHLORIDE.

ride reacts just like an acyl chloride; that is, the nucleophile attacks at the sulfur, displacing the electrons onto the oxygen. In the next step these electrons help to displace the leaving group.



Sulfurous acid

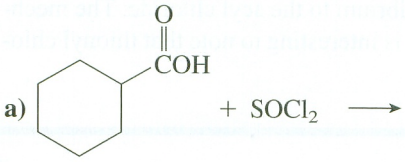


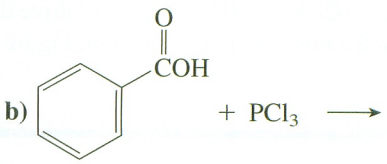
Thionyl chloride

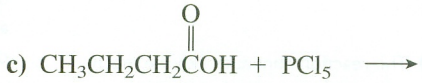
The major use for acyl chlorides is as starting materials for the preparation of the other carboxylic acid derivatives. Acyl fluorides, bromides, and iodides could potentially be employed to prepare the other derivatives also. However, because they offer no advantages over the acyl chlorides, they are seldom used.

PROBLEM 19.5

Show the products of these reactions:

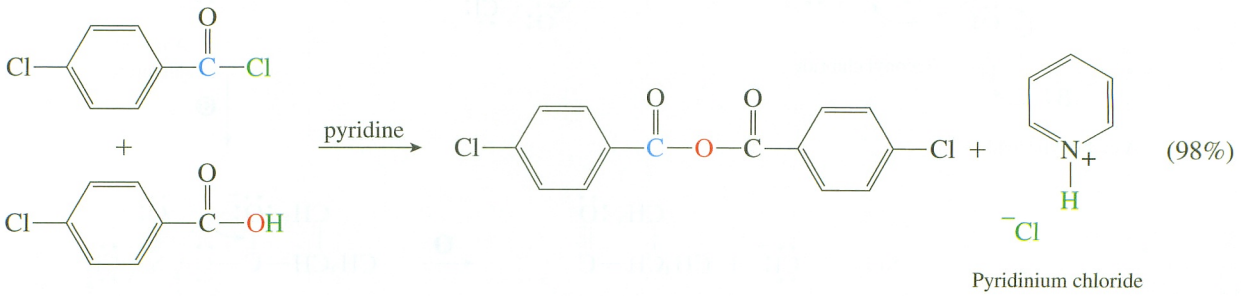






19.3 PREPARATION OF ANHYDRIDES

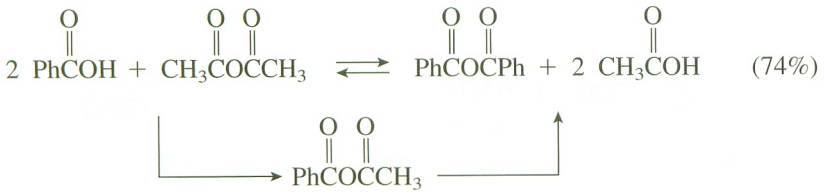
An anhydride can be prepared by the reaction of a carboxylic acid, or its conjugate base, with an acyl chloride as illustrated in the following equation:



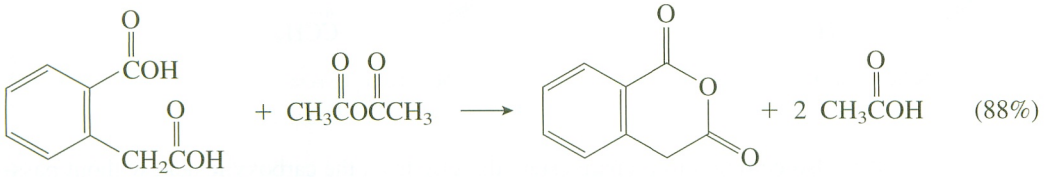
Pyridinium chloride

Pyridine is often added to these reactions, or used as a solvent, to react with the HCl that is produced and prevent the reaction mixture from becoming strongly acidic, which may cause decomposition and lower yields.

Anhydrides can also be prepared by the reaction of a carboxylic acid with another anhydride, usually acetic anhydride. A mixed anhydride is an intermediate in this reaction:

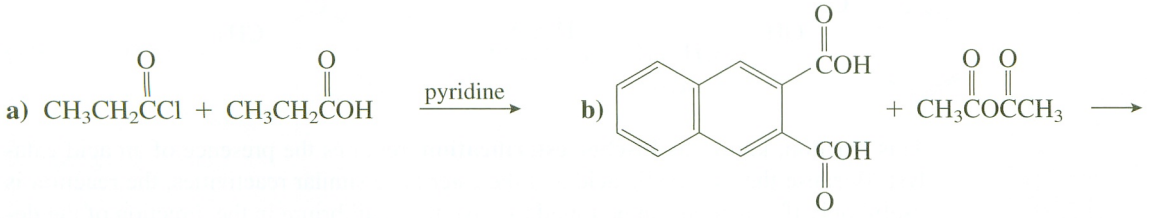


To make this preparation useful, the equilibrium is driven to the right by removal of the acetic acid by careful distillation. This is often the method of choice for the preparation of cyclic anhydrides, in which the equilibrium is favored by entropy:



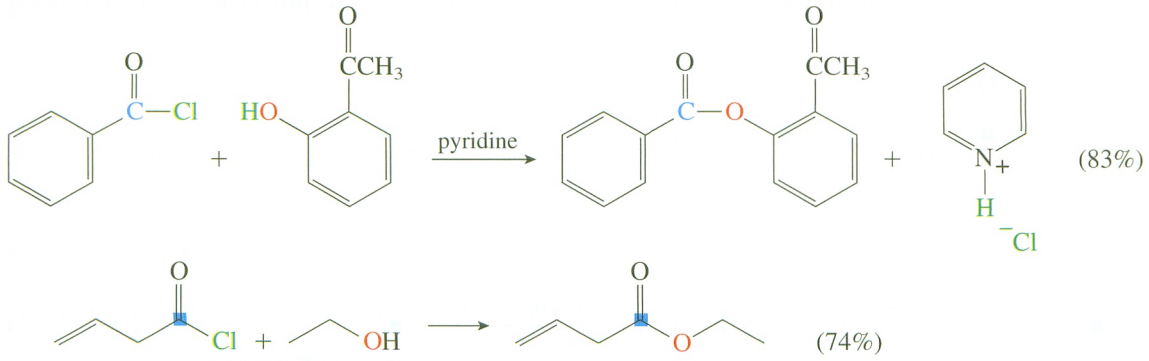
PROBLEM 19.6

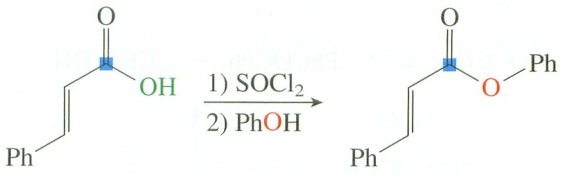
Show the products of these reactions:

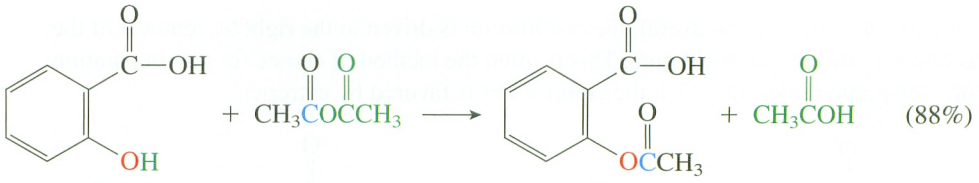


19.4 PREPARATION OF ESTERS

Esters are readily prepared by reaction of an alcohol with either an acyl chloride or an anhydride. Because it is more easily prepared from the acid, the acyl chloride is commonly employed. Again, a base, such as pyridine, is often added to react with the HCl that is produced. Acetic anhydride, which is commercially available, is often used for the preparation of acetate esters. Following are several examples.



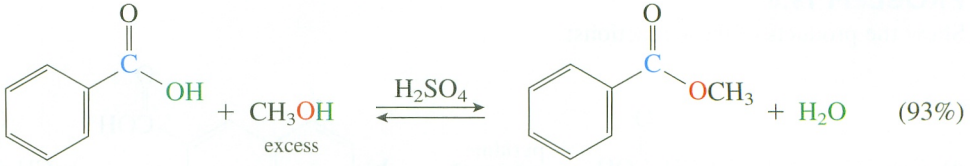




Salicylic acid

Acetylsalicylic acid (aspirin)

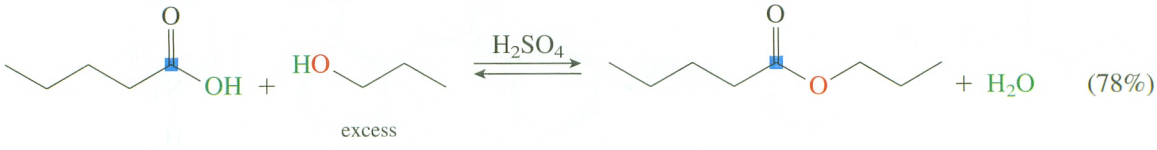
It is also common to prepare esters directly from the carboxylic acid without passing through the acyl chloride or the anhydride, as follows:



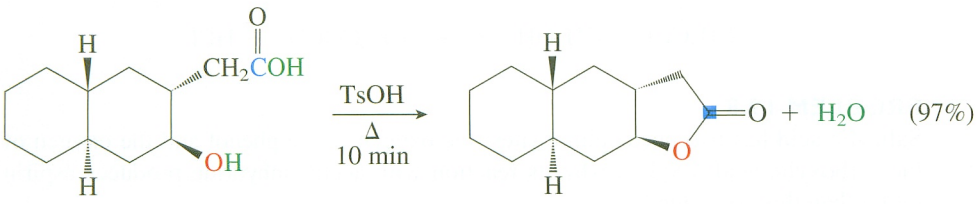
This reaction, known as **Fischer esterification,** requires the presence of an acid catalyst. Because the carboxylic acid and the ester have similar reactivities, the reaction is useful only if a method can be found to drive the equilibrium in the direction of the desired product—the ester. In accord with Le Chatelier's principle, this is accomplished by using an excess of one of the reactants or by removing one of the products. An excess of the alcohol is used if it is readily available, as is the case for methanol or ethanol. Or water can be removed by azeotropic distillation with a solvent such as toluene.

The mechanism for the Fischer esterification is shown in Figure 19.3. Sulfuric acid, hydrochloric acid, or *p*-toluenesulfonic acid is most often used as a catalyst. The mechanism will be easier to remember if you note the similarities to other acid-catalyzed mechanisms, such as the one for the formation of acetals in Figure 18.5. Also note that the steps leading from the tetrahedral intermediate to the carboxylic acid and alcohol starting materials and to the ester and water products are very similar.

Other examples of the Fischer esterification are provided by the following equations:



Lactones are cyclic esters. Their formation is very favorable when a hydroxy group and a carboxylic acid in the same molecule can react to form a five- or six-membered ring:



A lactone
(a cyclic ester)

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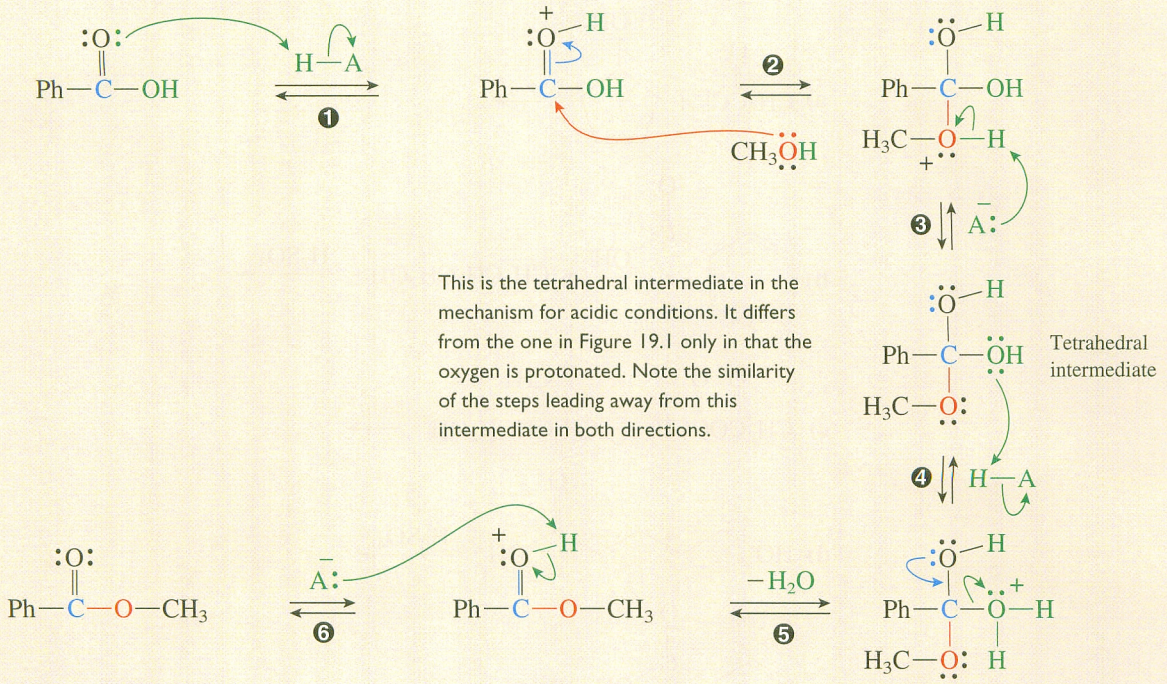
❶ Acid-catalyzed reactions begin by protonation of the oxygen of the carbonyl group to make the carbon more electrophilic.

❷ Then the nucleophile, the oxygen of the alcohol, bonds to the carbonyl carbon.

❸ Next, a proton is transferred to some base in the solution.



This is the tetrahedral intermediate in the mechanism for acidic conditions. It differs from the one in Figure 19.1 only in that the oxygen is protonated. Note the similarity of the steps leading away from this intermediate in both directions.

❻ Only a proton transfer is needed to complete the reaction. This step resembles the reverse of step 1. The acid, HA, is regenerated here, so the reaction is acid catalyzed.

❺ Then water leaves in a step that resembles the reverse of step 2.

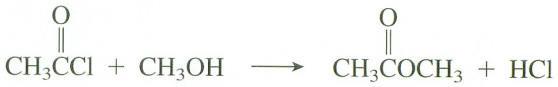
❹ Before the oxygen leaves, it is protonated to make it a better leaving group, water. This resembles the reverse of step 3.

Figure 19.3

MECHANISM OF FISCHER ESTERIFICATION.

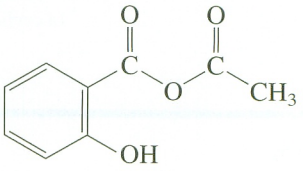
PROBLEM 19.7

Show all of the steps in the mechanism for this reaction:



PROBLEM 19.8

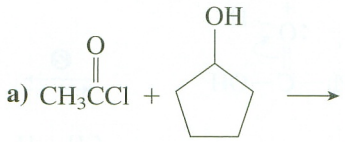
Salicylic acid has two nucleophilic sites: the oxygen of the phenol and the oxygen of the carboxylic acid. Explain why its reaction with acetic anhydride produces aspirin rather than this compound:



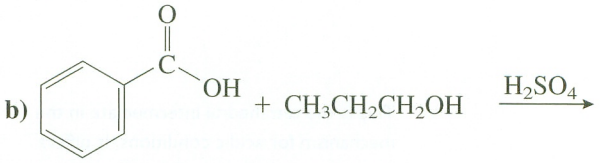
PROBLEM 19.9

Show the products of these reactions:

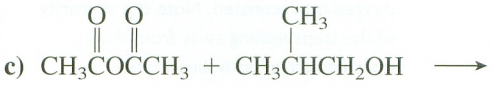
a)



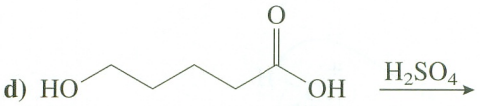
b)



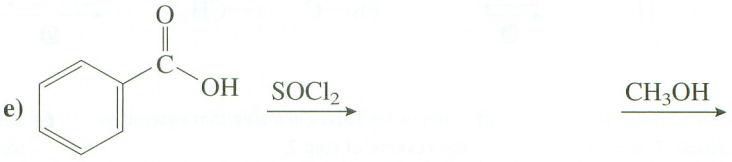
c)



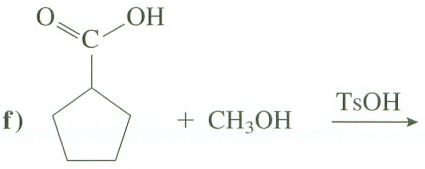
d)



e)



f)

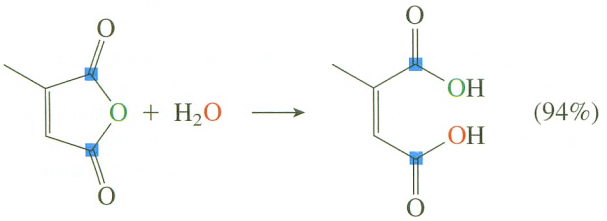


19.5 Preparation of Carboxylic Acids

Carboxylic acids commonly are used as the starting materials for the preparation of the other acid derivatives. However, any of the acid derivatives can be hydrolyzed to the carboxylic acid by reaction with water under the appropriate conditions. Acid or base catalysis is necessary for the less reactive derivatives.

Acyl Chloride and Anhydride Hydrolysis

Acyl chlorides and anhydrides must be protected from water because they react readily, often vigorously, with water to produce carboxylic acids. This reaction is not of much synthetic usefulness because the acyl chloride or anhydride is usually prepared from the acid. However, the hydrolysis reaction is occasionally used for the preparation of a carboxylic acid if the acyl chloride or anhydride is available from some other source. The following equation provides an example:



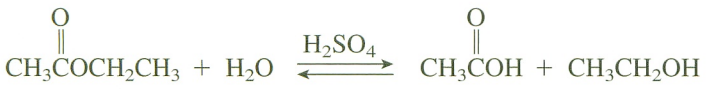
(94%)

Ester Hydrolysis

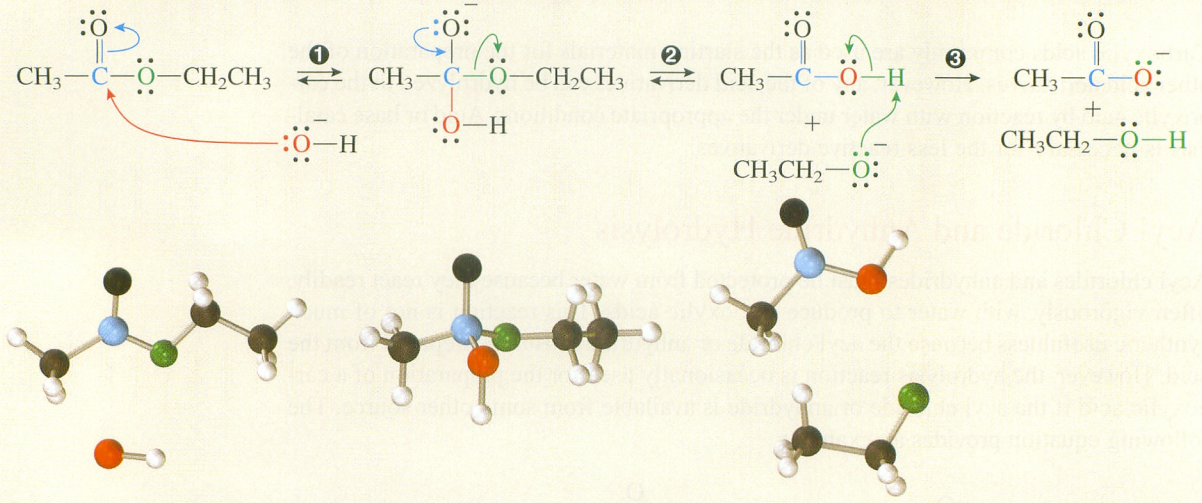
Esters can be hydrolyzed to carboxylic acids under either acidic or basic conditions. Under acidic conditions the mechanism is the exact reverse of the Fischer esterification mechanism shown in Figure 19.3. Again, because the acid and the ester have comparable reactivities, some method must be used to drive the equilibrium toward the desired product—the acid in this case. This can be accomplished by using water as the solvent, providing a large excess of this reagent that, by Le Chatelier's principle, shifts the equilibrium toward the carboxylic acid.

PROBLEM 19.10

Show all of the steps in the mechanism for this reaction:



It is more common to hydrolyze esters under basic conditions because the equilibrium is favorable. The mechanism for this process, called **saponification,** is presented in Figure 19.4. The production of the conjugate base of the carboxylic acid, the carboxylate anion, which is at the bottom of the reactivity scale, drives the equilibrium in the desired direction. To isolate the carboxylic acid, the solution must be acidified after the hydrolysis is complete. Some examples are provided in the following equations. We saw another example of this hydrolysis reaction in Chapter 10, where it was



❶ This step is the same as the first step of Figure 19.1. The nucleophile, hydroxide ion in this case, bonds to the carbonyl carbon, displacing the pi electrons onto the oxygen.

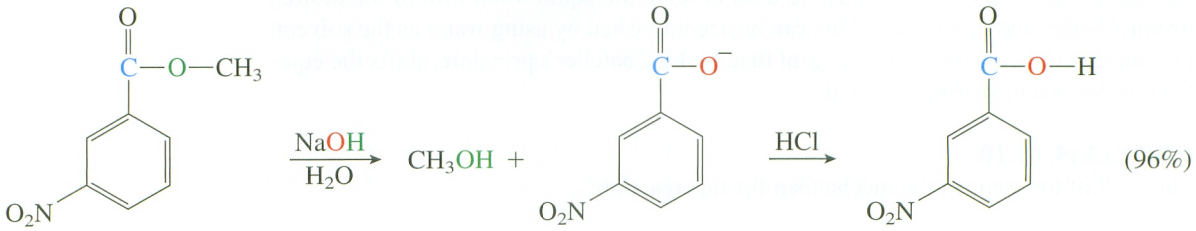
❷ Next, the leaving group, ethoxide ion, departs as an electron pair from the negative oxygen reforms the double bond of the carbonyl group.

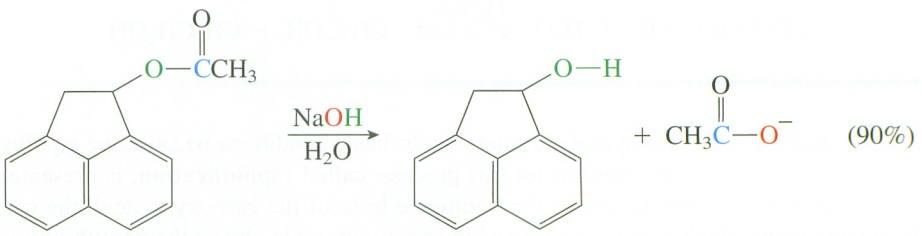
❸ Ethoxide ion, a strong base, removes a proton from acetic acid. The formation of the weak base, acetate ion, in this step drives the equilibrium to the final products, the alcohol and the carboxylate anion.

Figure 19.4

MECHANISM OF THE BASE-CATALYZED HYDROLYSIS (SAPONIFICATION) OF AN ESTER.

used in the preparation of alcohols by the acetate method (see Section 10.2 and Figure 10.1 on page 351).





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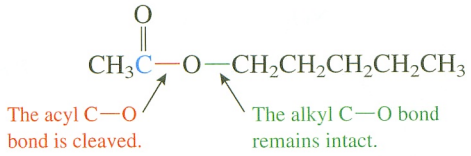
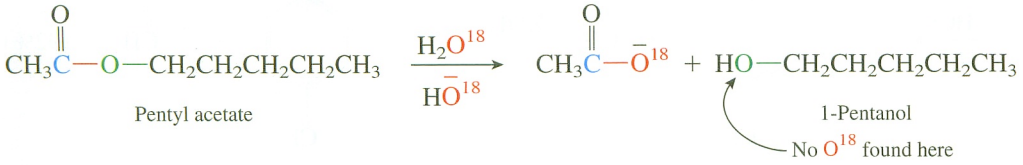
As we have seen before, a variety of experiments are used to support or disprove a mechanism that has been postulated for a particular reaction. The mechanism for the basic hydrolysis of esters, shown in Figure 19.4, involves cleavage of the bond between

the ether oxygen of the ester and the carbonyl carbon rather than the cleavage of the bond between this oxygen and the carbon of the alcohol part of the ester.



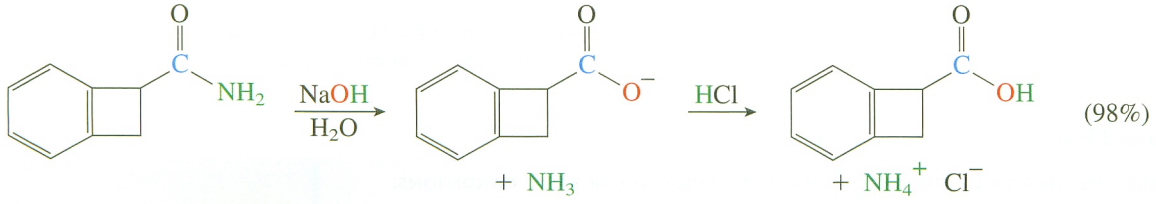
Proof that it is indeed this bond that is cleaved was provided by conducting the hydrolysis in water with an enriched content of ^{18}O. Pentyl acetate was hydrolyzed in this isotopically enriched water. The 1-pentanol product was shown by mass spectrometry to contain only the normal amount of ^{18}O, demonstrating that the alkyl C—O bond was not broken during the reaction.

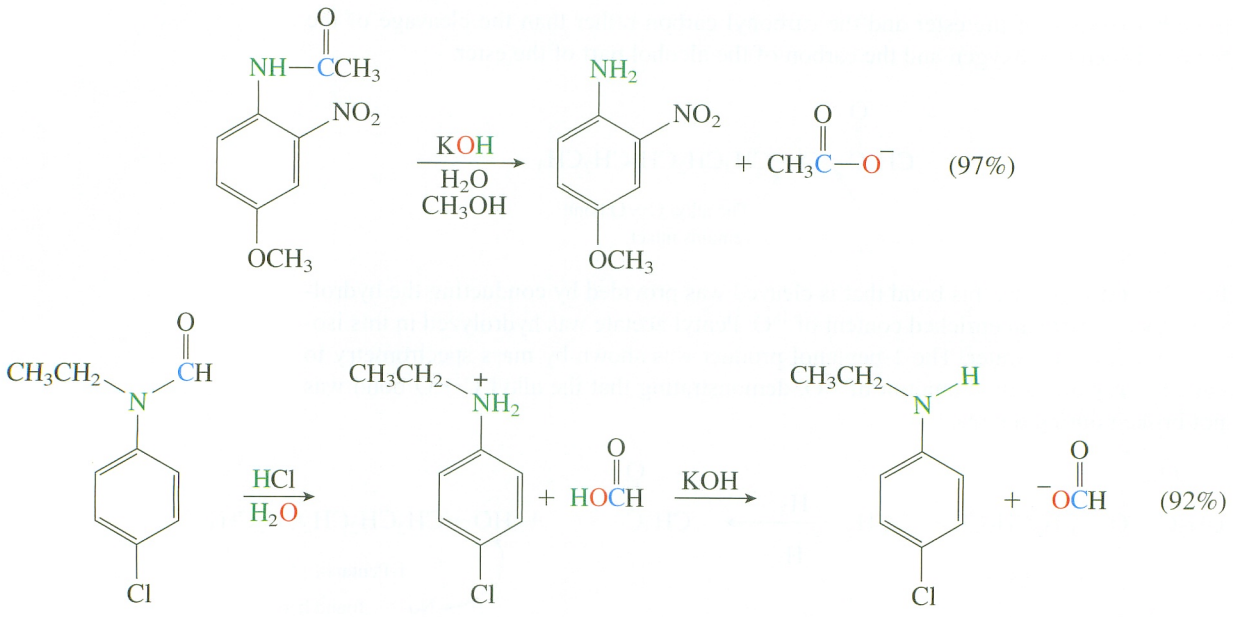


Amide Hydrolysis

Amides are less reactive than esters, and their hydrolysis often requires vigorous heating in either aqueous acid or base. The mechanism for acidic conditions is quite similar to the reverse of the Fischer esterification mechanism shown in Figure 19.3. The mechanism for basic conditions is related to that depicted in Figure 19.4 for ester saponification and a similar tetrahedral intermediate is formed in the first step. However, NH_2^- is a strong base and a poor leaving group, so the nitrogen must usually be protonated before it can leave. The exact timing of the various proton transfers that occur in this mechanism (and many others) is difficult to establish and depends on both the structure of the amide and the reaction conditions. One possible mechanism is shown in Figure 19.5.

Under acidic conditions the equilibrium for the hydrolysis of an amide is driven toward the products by the protonation of the ammonia or amine that is formed. Under basic conditions the equilibrium is driven toward the products by the formation of the carboxylate anion, which is at the bottom of the reactivity scale. The pH of the final solution may need to be adjusted, depending on which product is to be isolated. If the carboxylic acid is desired, the final solution must be acidic, whereas isolation of the amine requires that the solution be basic. Several examples are shown in the following equations. Also, note that the last step of the Gabriel amine synthesis, the hydrolysis of the phthalimide (see Section 10.6 and Figure 10.5 on page 365), is an amide hydrolysis.

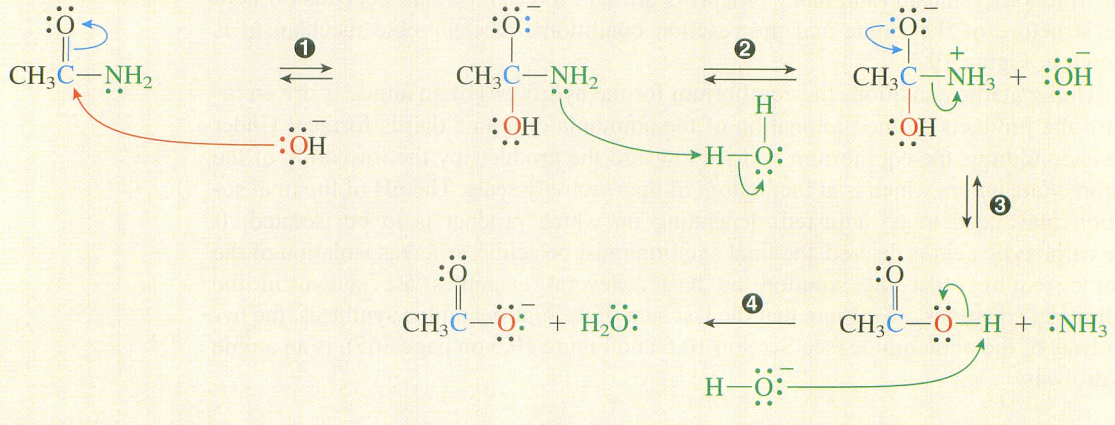




❶ A hydroxide ion nucleophile bonds to the carbon of the carbonyl group, exactly as the mechanism for the saponification of an ester begins.

❷ At this point, this mechanism deviates slightly from the ester saponification mechanism. Because amide ion (NH_2^-) is a poor leaving group, the nitrogen is first protonated by the solvent to convert it to a better leaving group.

❸ Ammonia leaves while an electron pair from the negative oxygen reforms the double bond of the carbonyl group.



❹ A proton transfer from the carboxylic acid to a hydroxide ion completes the process.

Figure 19.5

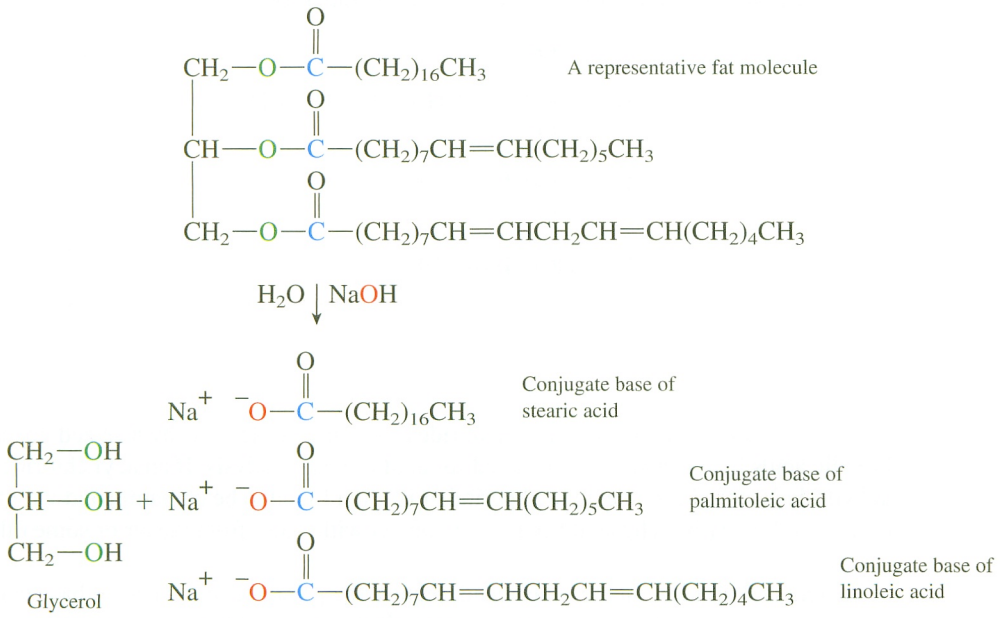
POSSIBLE MECHANISM OF THE HYDROLYSIS OF AN AMIDE UNDER BASIC CONDITIONS.

Focus On

The Preparation of Soap

The preparation of a solution of soap by the reaction of fat with water in the presence of base was probably one of the earliest chemical processes discovered by humans. Although the details of this discovery are lost in antiquity, we can imagine early humans finding that water that had been in contact with wood ashes from the campfire could be used to remove grease from hands and other objects and that this water became a more effective cleaning agent as it was used. The water leaches some alkaline compounds from the ashes, and this basic water hydrolyzes the esters of the fat or grease to alcohols and soap. This is why the hydrolysis of esters under basic conditions is called saponification (the Latin word for soap is *sapo*).

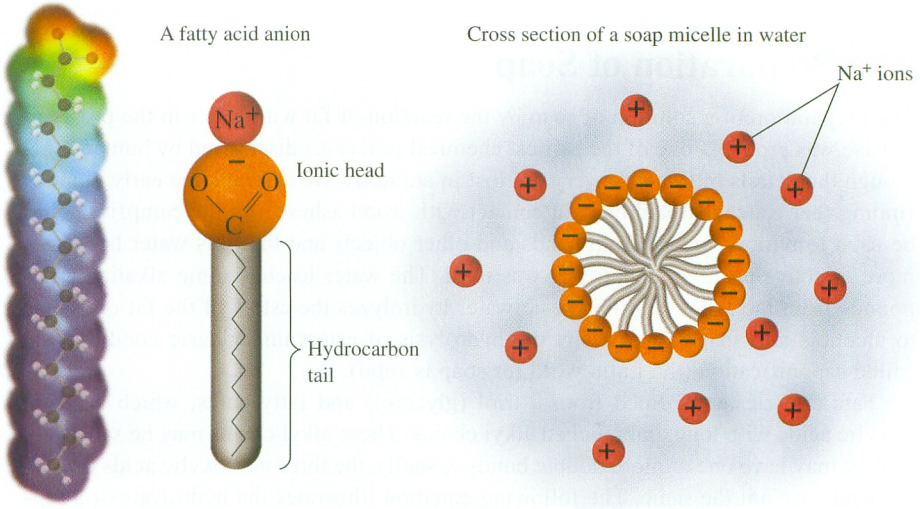
Fats are triesters formed from a triol (glycerol) and fatty acids, which are carboxylic acids with long, unbranched alkyl chains. These alkyl chains may be saturated, or they may have one or more double bonds. Usually, the three carboxylic acids of a fat molecule are not the same. The following equation illustrates the hydrolysis of a representative fat molecule to glycerol and the conjugate bases of stearic acid, palmitoleic acid, and linoleic acid. Addition of NaCl causes the fatty acid salts to precipitate. The resulting solid is formed into bars of soap.



The cleaning action of soap is due to the dual nature of the conjugate base of the fatty acid molecule. On one end is the ionic carboxylate anion group; the rest of the molecule consists of a nonpolar hydrocarbon chain. The ionic part, called the head, is attracted to a polar solvent such as water and is hydrophilic, whereas the long hydrocarbon tail is hydrophobic. In water, soap molecules tend to group together in clusters called micelles, with their ionic heads oriented toward the water molecules and their hydrocarbon tails in the interior of the cluster so that unfavorable interactions with water are avoided. Non-

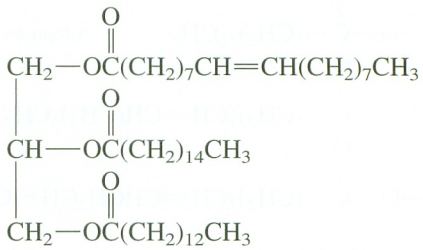
Continued

polar grease and fat molecules dissolve in the interior of the micelle. The ionic heads keep the micelle in solution and allow water to wash it away, along with the grease.



PROBLEM 19.11

Show the products that are formed when this fat is saponified:

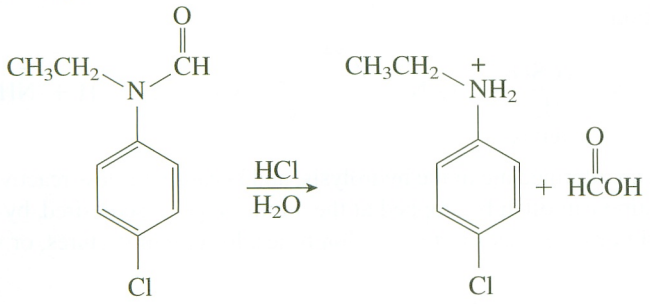


As mentioned previously, acyl chlorides and anhydrides are hydrolyzed to carboxylic acids by water without the need for acid or base catalysis. If an acyl chloride or anhydride is stored for an extended period, it is often found to be contaminated with the corresponding carboxylic acid because of contact with water from the air or some other source.

Esters and amides, on the other hand, require the presence of an acid or base catalysis to react with water. These reactions are not instantaneous but require rather strongly acidic or basic conditions and heat to proceed at a reasonable rate. For example, a typical ester saponification is usually conducted with 10% NaOH in water, and the solution is refluxed until the ester layer disappears. (Most esters are not soluble in water.) This may require from 15 minutes up to several hours of reflux. Similarly, a typical amide hydrolysis is often conducted by refluxing the amide in concentrated hydrochloric acid for a period ranging from 15 minutes up to several hours. Esters and amides are relatively stable to the near-neutral conditions found in living organisms, which is one reason why they are important functional groups in biochemistry.

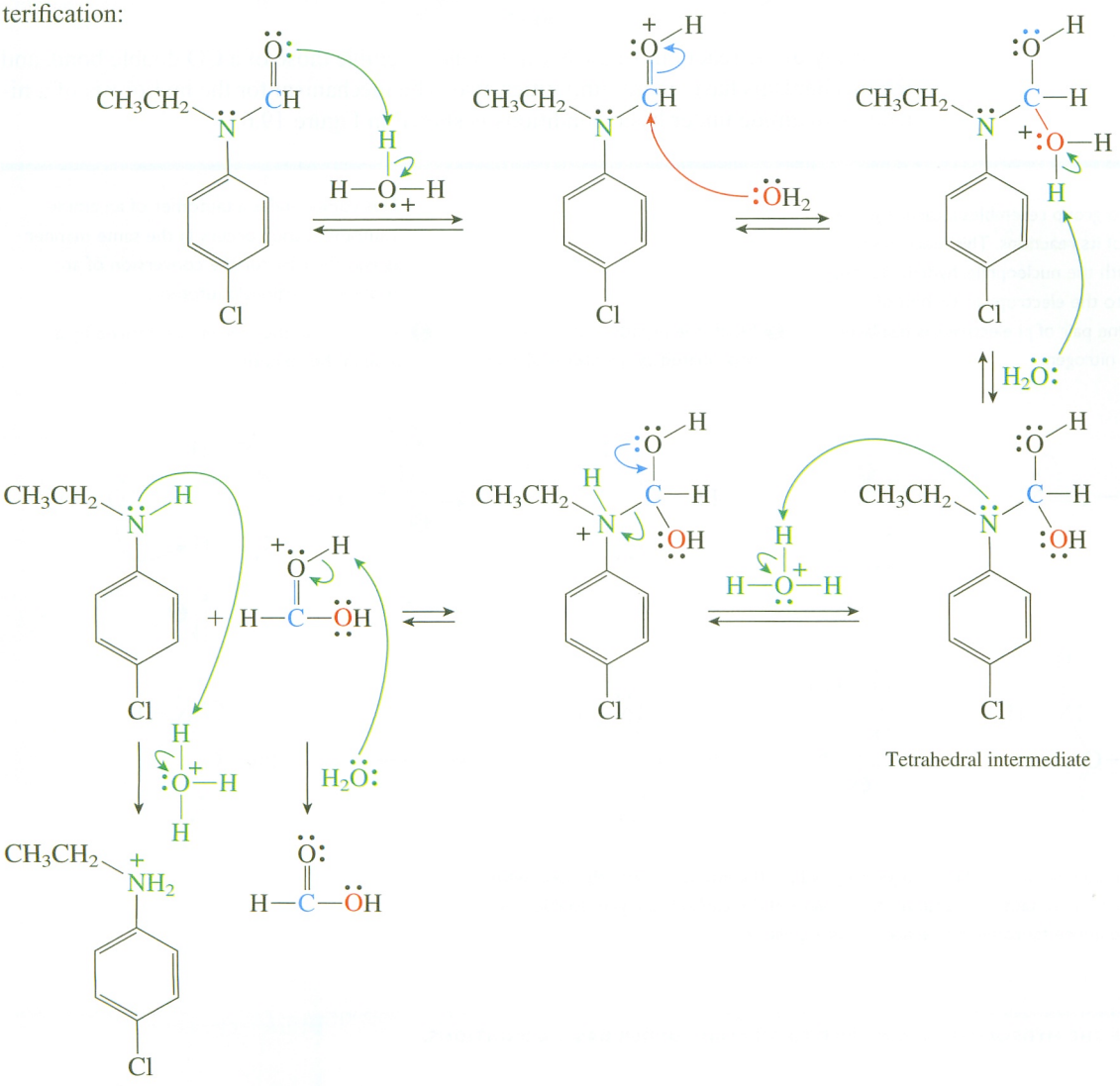
PRACTICE PROBLEM 19.2

Show all of the steps in the mechanism for this reaction:



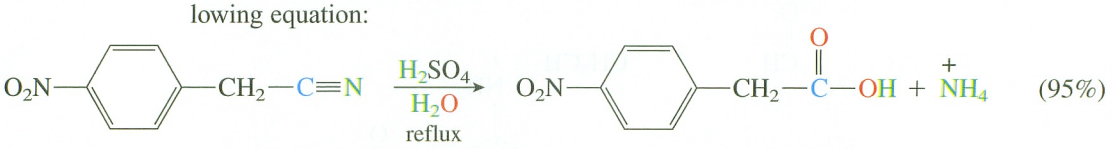
Solution

This acid-catalyzed mechanism resembles the reverse of the mechanism for Fischer esterification:

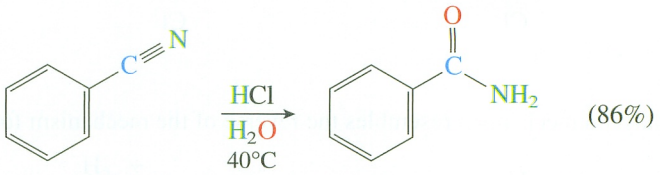


Nitrile Hydrolysis

Nitriles are often considered as derivatives of carboxylic acids because they can be hydrolyzed to the carboxylic acid under acidic or basic conditions, as illustrated in the following equation:



The amide is an intermediate in the hydrolysis, and because it is less reactive than the nitrile, the reaction can often be stopped at the amide stage, if so desired, by using milder reaction conditions, such as shorter reaction times, lower temperatures, or weaker base:

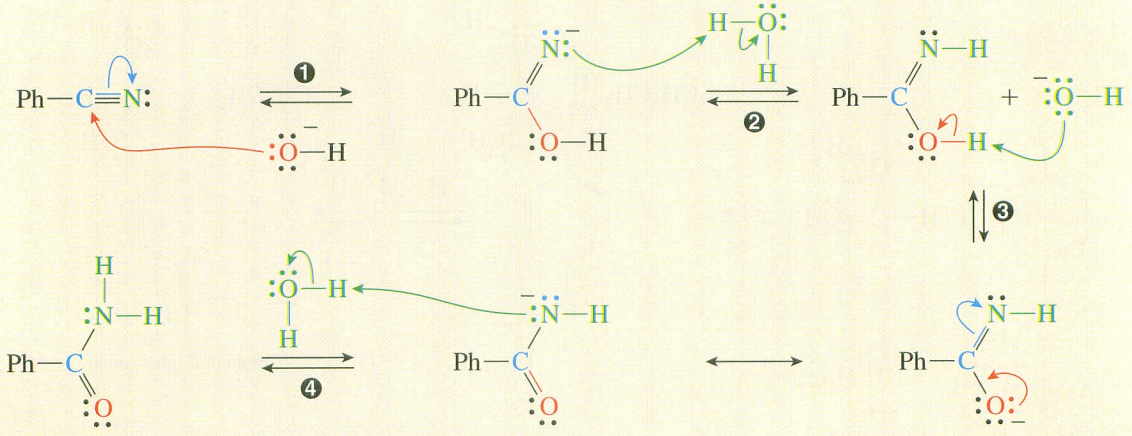


Many of the reactions of a CN triple bond resemble those of a CO double bond, and the mechanisms have many similarities also. The mechanism for the hydrolysis of a nitrile to an amide under basic conditions is shown in Figure 19.6.

❶ The cyano group resembles a carbonyl group in many of its reactions. This mechanism begins with the nucleophile, hydroxide ion, bonding to the electrophilic carbon of the nitrile. One pair of pi electrons is displaced onto the nitrogen.

❷ Next, the negative nitrogen is protonated by a water molecule.

❸ A proton on the oxygen is removed by a base in the solution. This compound is a tautomer of an amide. Tautomerization occurs in the same manner as was the case for the conversion of an enol to its carbonyl tautomer.

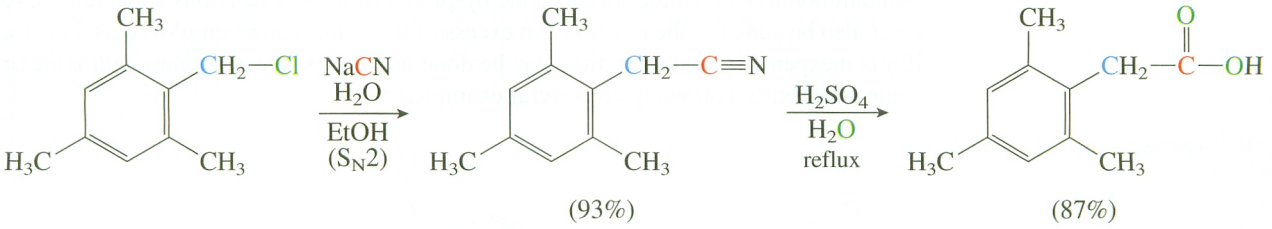


❹ Reprotonation occurs on the nitrogen to produce the amide. As was the case with the carbonyl–enol tautomerization, the stability of the carbon–oxygen double bond causes the amide tautomer to be favored at equilibrium.

Figure 19.6

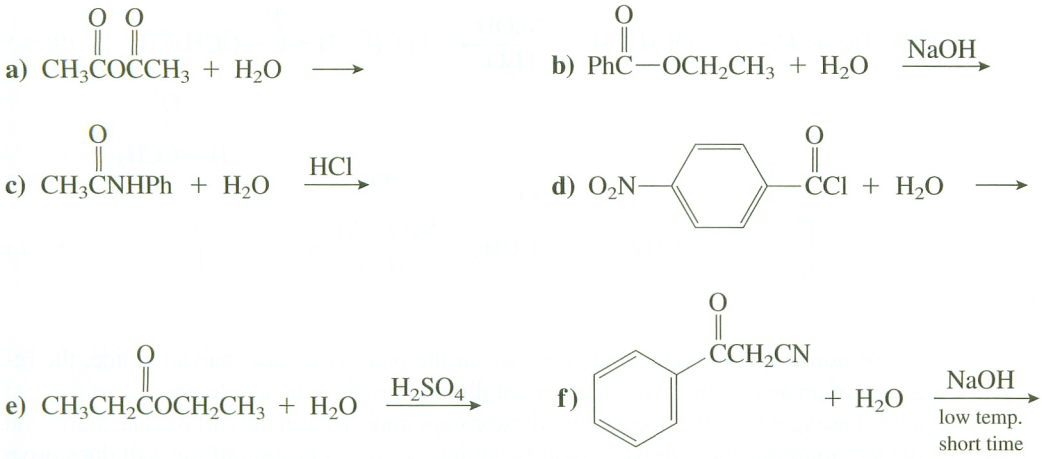
MECHANISM OF THE HYDROLYSIS OF A NITRILE TO AN AMIDE UNDER BASIC CONDITIONS.

The use of cyanide ion as a nucleophile in an S_N2 reaction (see Section 10.8), followed by hydrolysis of the product nitrile, provides a useful preparation of carboxylic acids that contain one more carbon than the starting compound:



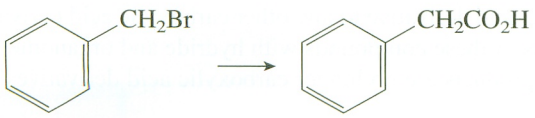
PROBLEM 19.12

Show the products of these reactions:



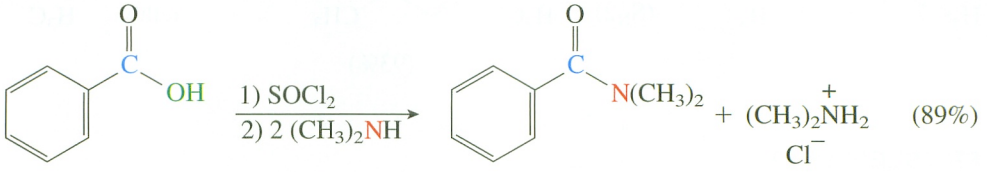
PROBLEM 19.13

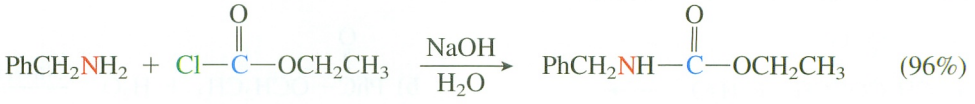
Suggest a synthesis of 2-phenylacetic acid from benzyl bromide:

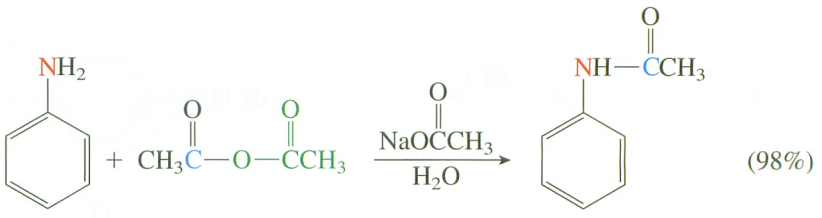


19.6 PREPARATION OF AMIDES

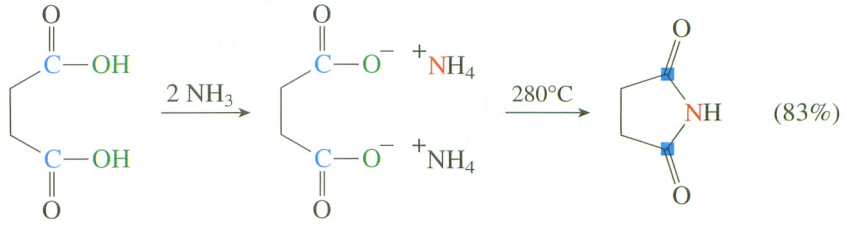
Amides are most commonly prepared by reaction of an acyl chloride or an anhydride with ammonia or an amine. Because the by-products of these reactions are acidic, base must also be added to the reaction. An excess of the amine can be employed as the base if it is inexpensive, or the reaction may be done in the presence of sodium hydroxide or some other base. Following are several examples.







Although a carboxylic acid is higher on the reactivity scale than an amide, the reaction of an acid with an amine does not directly produce the amide because of the fast acid–base reaction that occurs with these compounds to form the carboxylate anion and the ammonium cation derived from the amine. Vigorous heating of this salt does drive off water to produce the amide, but this procedure is seldom of preparative value except for the formation of **cyclic amides** (called **lactams**) containing five or six atoms in the ring. The following equation shows such a reaction of a dicarboxylic acid to form two amide bonds, producing a cyclic **imide:**

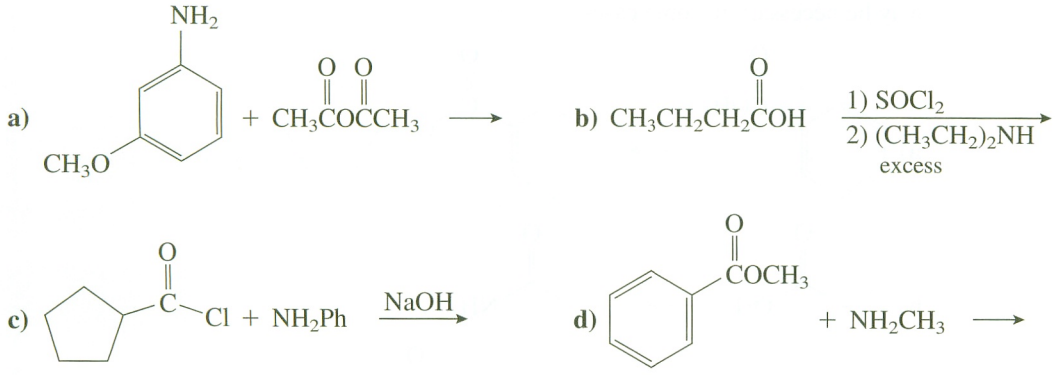


An imide

By using the reactions described in Sections 19.2 through 19.6, it is possible to convert one carboxylic acid derivative to any other carboxylic acid derivative. Now let's examine the reactions of these compounds with hydride and organometallic nucleophiles. In these cases the products are no longer carboxylic acid derivatives.

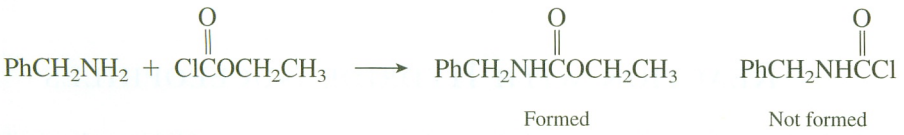
PROBLEM 19.14

Show the products of these reactions:



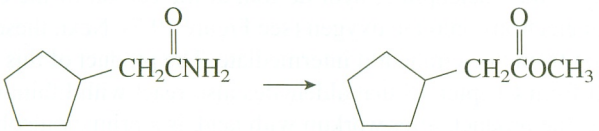
PROBLEM 19.15

Show all of the steps in the mechanism for this reaction and explain why the indicated product is formed and the other is not:



PRACTICE PROBLEM 19.3

Suggest reactions that could be used to convert this amide to the methyl ester:

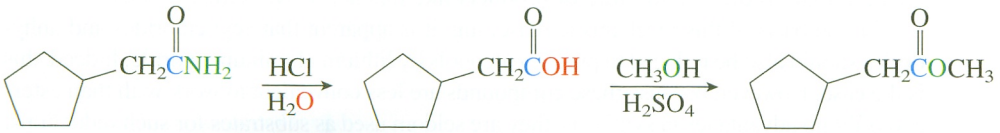


Strategy

Any carboxylic acid derivative can be converted to any other using one or more of the reactions discussed in the previous sections. If the conversion requires going from a less reactive derivative to a more reactive one, then an indirect route may be necessary. Remember that any derivative can be hydrolyzed to a carboxylic acid using water and acid or base. Also remember that the carboxylic acid can be converted to the acyl chloride with thionyl chloride, providing access to the other derivatives.

Solution

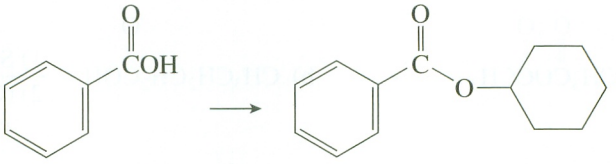
There is no reaction that directly converts an amide to an ester because the amide is less reactive. Therefore, the amide is first hydrolyzed to the acid and then the acid is esterified:



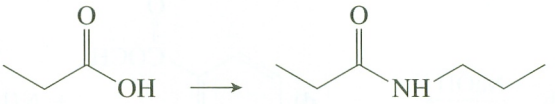
PROBLEM 19.16

Suggest reactions that would accomplish these transformations. More than one step may be necessary in some cases.

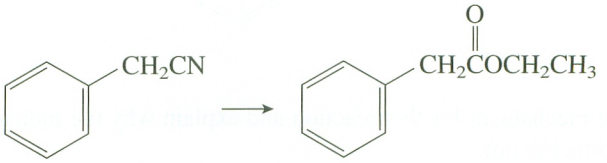
a)



b)



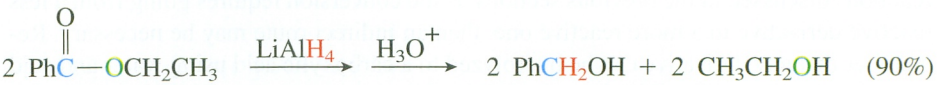
c)



19.7 Reaction with Hydride Nucleophiles

On the basis of what we have already learned about the reactions of lithium aluminum hydride with aldehydes and ketones (Chapter 18) and the mechanisms presented so far in this chapter, we can readily predict the product that results when hydride reacts with a carboxylic acid derivative. Consider, for example, the reaction of ethyl benzoate with lithium aluminum hydride. As with all of the reactions in this chapter, this reaction begins with attack of the nucleophile, hydride ion, at the carbon of the carbonyl group, displacing the pi electrons onto the oxygen (see Figure 19.7). Next, these electrons help displace ethoxide from the tetrahedral intermediate. The product of this step is an aldehyde. But recall from Chapter 18 that aldehydes also react with lithium aluminum hydride. Therefore, the product, after workup with acid, is a primary alcohol.

From the mechanism it can be seen that it takes two hydride nucleophiles to accomplish this reduction. Therefore, 1 mole of lithium aluminum hydride will reduce 2 moles of the ester.



What happens if less hydride reagent is used? Even though the aldehyde is produced first in the mechanism, the reaction cannot be stopped at the aldehyde stage because the aldehyde is higher on the reactivity scale than the ester. The aldehyde reacts with the hydride nearly as fast as it is formed. If less than 1 mole of hydride per 2 moles of ester is used, a mixture of the ester and the alcohol is produced, along with some of the aldehyde. A reaction that produces a mixture of products like this is not synthetically useful.

On the basis of this mechanistic reasoning, it is apparent that acyl chlorides and anhydrides should also be reduced to primary alcohols by lithium aluminum hydride. Indeed, this is the case. However, because these compounds are less convenient to work with than esters and offer no advantages in synthesis, they are seldom used as substrates for such reductions.

Carboxylic acids are also reduced to primary alcohols by lithium aluminum hydride. The first step in the mechanism for this reaction is an acid–base reaction between the

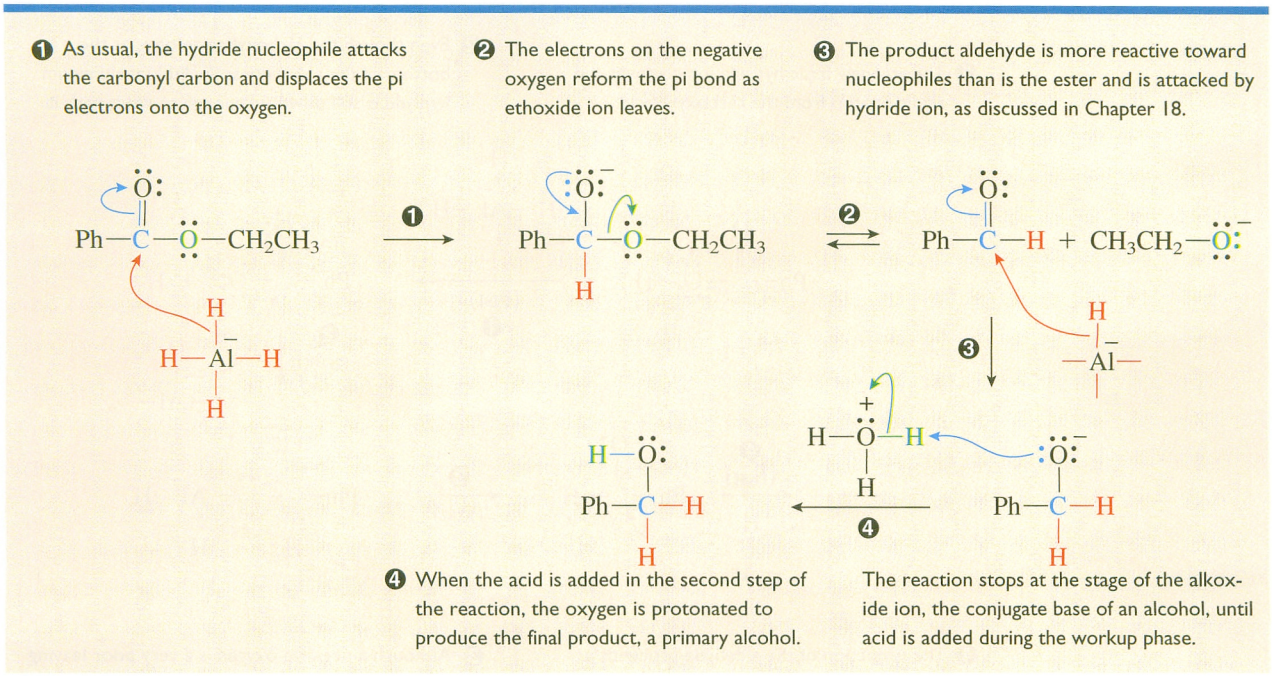
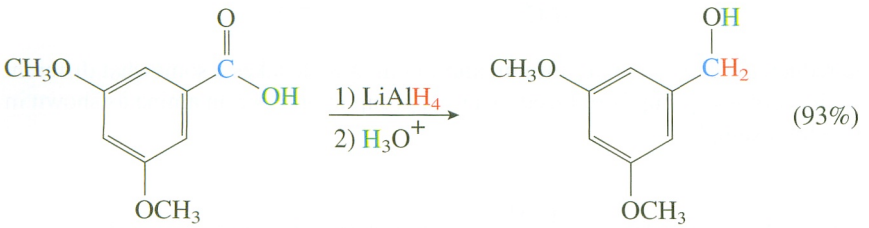

❶ As usual, the hydride nucleophile attacks the carbonyl carbon and displaces the pi electrons onto the oxygen.
❷ The electrons on the negative oxygen reform the pi bond as ethoxide ion leaves.
❸ The product aldehyde is more reactive toward nucleophiles than is the ester and is attacked by hydride ion, as discussed in Chapter 18.
❹ When the acid is added in the second step of the reaction, the oxygen is protonated to produce the final product, a primary alcohol.
The reaction stops at the stage of the alkoxide ion, the conjugate base of an alcohol, until acid is added during the workup phase.

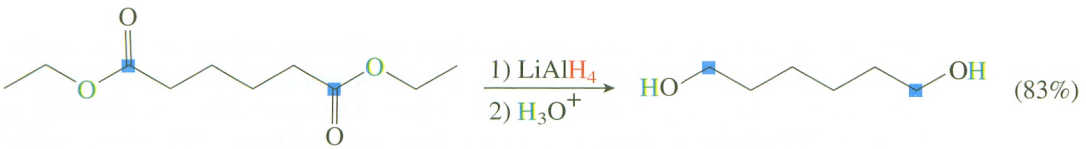
Figure 19.7

MECHANISM OF THE REDUCTION OF AN ESTER WITH LITHIUM ALUMINUM HYDRIDE.

hydride and the acid, as shown in Figure 19.8. Lithium aluminum hydride is reactive enough to attack the relatively unreactive carbonyl group of the carboxylate anion. For the reaction to proceed further, one of the negatively charged oxygens must act as a leaving group. The oxygen is assisted in this process by Lewis acid–base coordination with aluminum. This makes the oxygen less basic and better able to leave. (Similar Lewis acid–base coordination occurs in many other reactions. This is usually ignored in this text unless it makes a particularly important contribution to the reaction.)

In summary, reductions of carboxylic acid derivatives to primary alcohols are usually accomplished by reaction of esters or acids with lithium aluminum hydride. The following equations provide several examples:





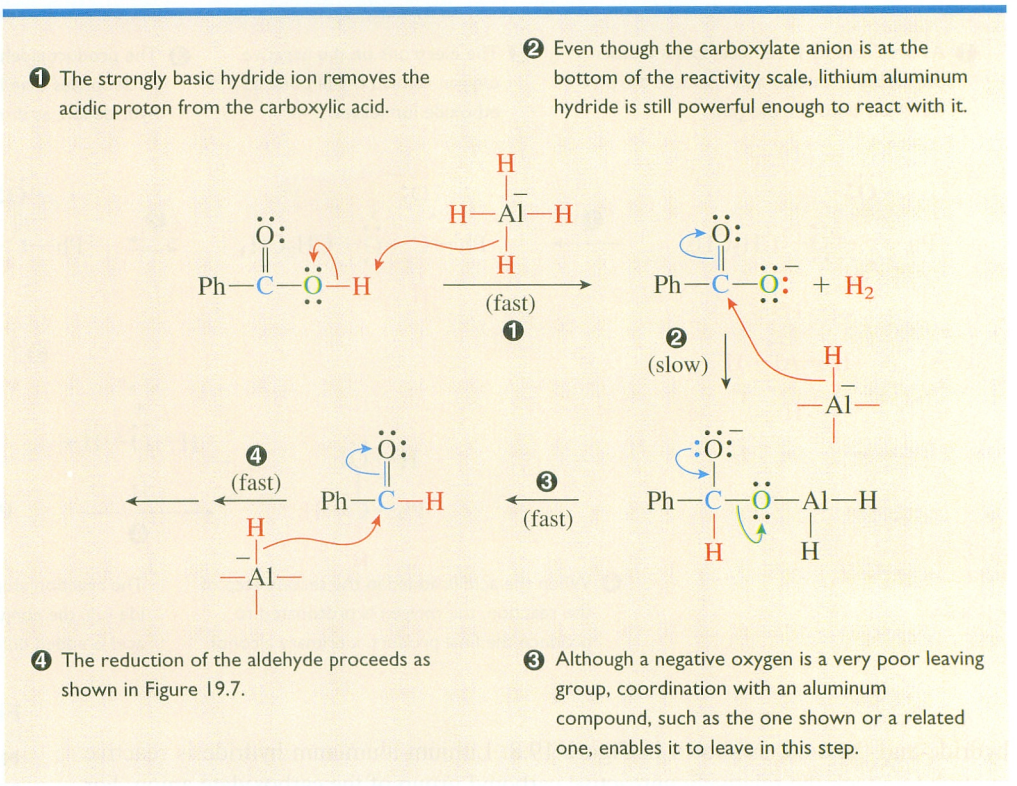
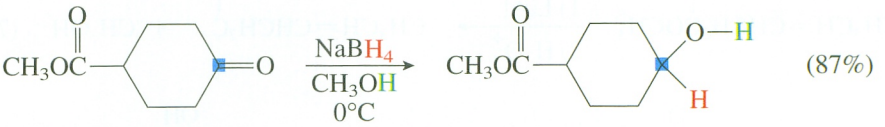

1 The strongly basic hydride ion removes the acidic proton from the carboxylic acid.
2 Even though the carboxylate anion is at the bottom of the reactivity scale, lithium aluminum hydride is still powerful enough to react with it.
(fast)
(slow)
(fast)
(fast)
4 The reduction of the aldehyde proceeds as shown in Figure 19.7.
3 Although a negative oxygen is a very poor leaving group, coordination with an aluminum compound, such as the one shown or a related one, enables it to leave in this step.

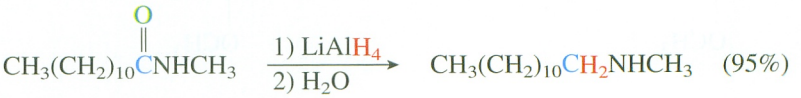
Figure 19.8

MECHANISM OF THE REDUCTION OF A CARBOXYLIC ACID WITH LITHIUM ALUMINUM HYDRIDE—THE FIRST STEPS.

Sodium borohydride is much less reactive than lithium aluminum hydride and reacts only slowly with esters, so it is seldom used for their reduction. However, this property can be used to advantage when we want to reduce an aldehyde or ketone group without reducing an ester group in the same compound.



The reduction of amides with lithium aluminum hydride takes a somewhat different course. The carbonyl group is reduced to a CH_2 group to produce an amine as shown in the following example:

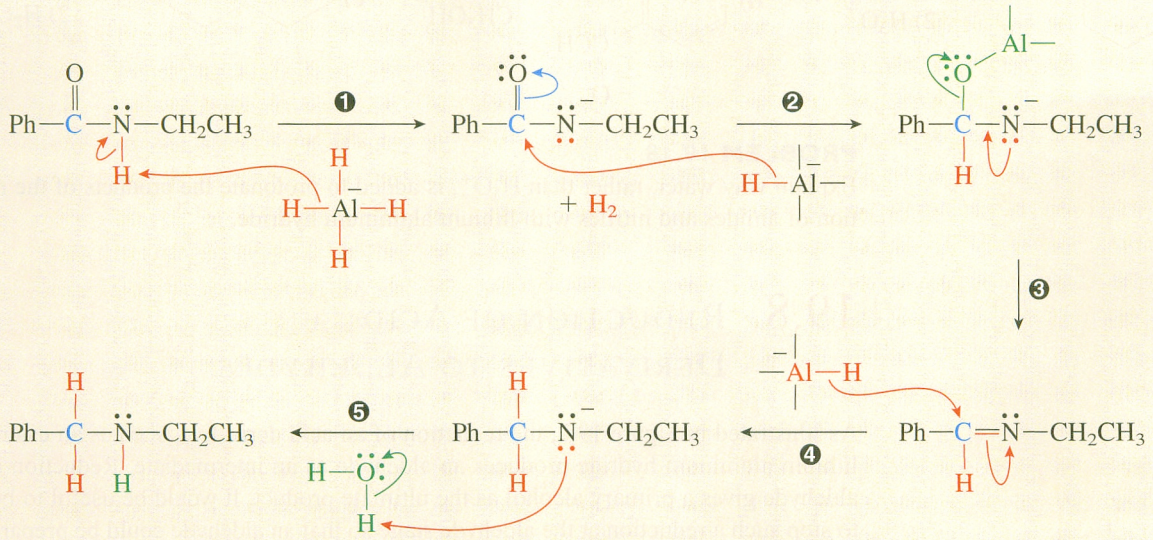


Although this reaction may look strange at first, it follows essentially the same mechanism as the reduction of a carboxylic acid. But the oxygen leaves rather than the nitrogen because the oxygen group is less basic. The mechanism is outlined in Figure 19.9. Note the similarity of this mechanism to that of Figure 19.8. The reduction

❶ Like the reaction shown in Figure 19.8, the mechanism begins with the basic hydride ion removing an acidic proton. Here, it is the proton on the nitrogen.

❷ Next, another hydride ion acts as a nucleophile, attacking the carbon of the carbonyl group.

❸ The oxygen, coordinated with aluminum, leaves in this step rather than the nitrogen because the oxygen is a weaker base and therefore a better leaving group.



❺ The final step in the mechanism is protonation of the negative nitrogen by water that is added during the workup.

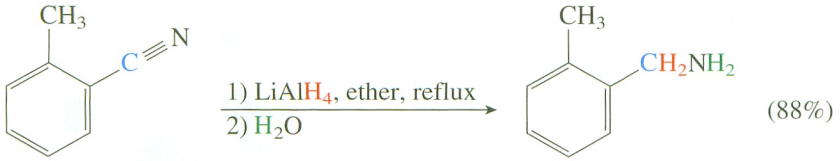
❹ The carbon–nitrogen double bond of the imine is attacked by the hydride nucleophile just like a carbon–oxygen double bond.

Figure 19.9

MECHANISM OF THE REDUCTION OF AN AMIDE TO AN AMINE BY LITHIUM ALUMINUM HYDRIDE.

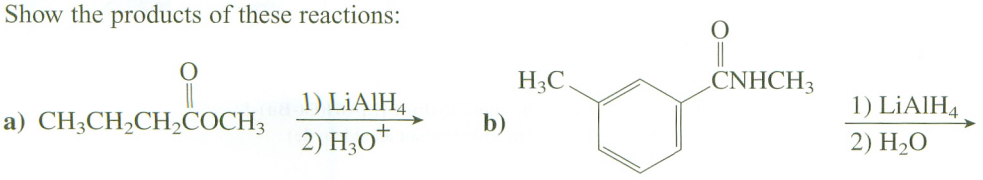
of amides with lithium aluminum hydride provides an important method for the preparation of amines. Primary, secondary, or tertiary amines can be prepared in this manner.

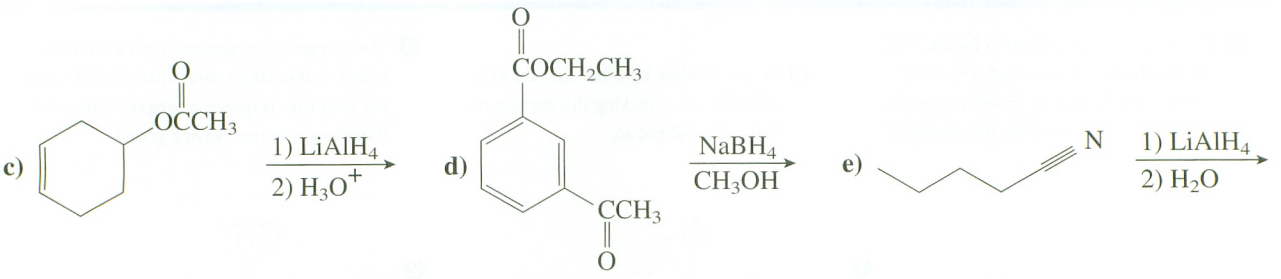
Another method that can be used to prepare primary amines is the reduction of nitriles with lithium aluminum hydride. The mechanism for this reaction involves sequential addition of two hydride nucleophiles to the electrophilic carbon of the cyano group. The addition of water in the workup step supplies the two protons on the nitrogen in the product. An example follows:



PROBLEM 19.17

Show the products of these reactions:





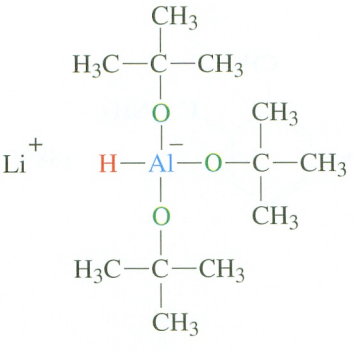
PROBLEM 19.18

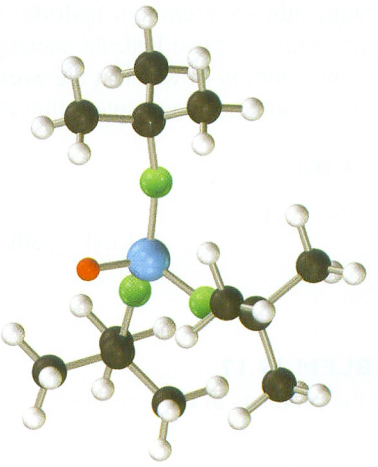
Explain why water, rather than H_3O^+, is added to protonate the products of the reduction of amides and nitriles with lithium aluminum hydride.

19.8 Reduction of Acid Derivatives to Aldehydes

As illustrated in Figure 19.7, the reduction of an acid derivative, such as an ester, with lithium aluminum hydride produces an aldehyde as an intermediate. Reduction of the aldehyde gives a primary alcohol as the ultimate product. It would be useful to be able to stop such a reduction at the aldehyde stage so that an aldehyde could be prepared directly from a carboxylic acid derivative.

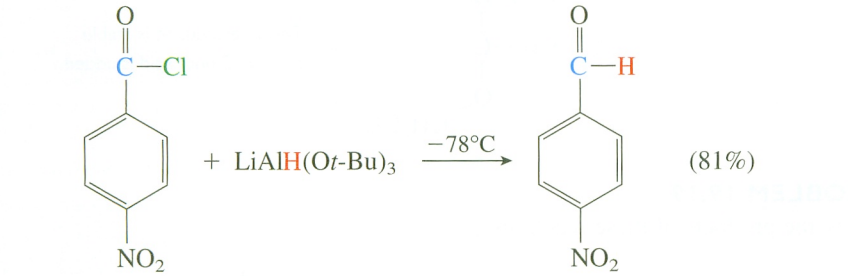
Let's analyze how such a conversion might be accomplished. What carboxylic acid derivative might be a suitable starting material for reduction to an aldehyde? An ester does not appear to be a good choice because it is less reactive than an aldehyde. Any reagent that is reactive enough to reduce the ester will also be reactive enough to reduce the aldehyde product. However, a more reactive carboxylic acid derivative, such as an acyl chloride, might prove suitable. An acyl chloride is more reactive than an aldehyde, so it is possible, at least in theory, to find a reducing agent that is reactive enough to reduce the acyl chloride but not reactive enough to reduce the aldehyde product. In fact, lithium tri-*t*-butoxyaluminum hydride, $LiAlH(Ot\text{-}Bu)_3$, has been found to have just such reactivity:

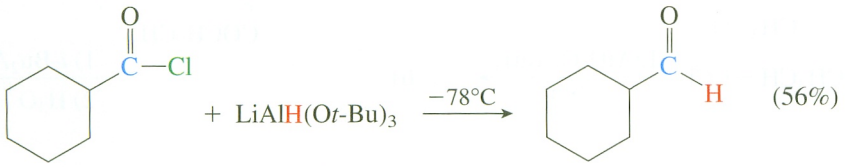




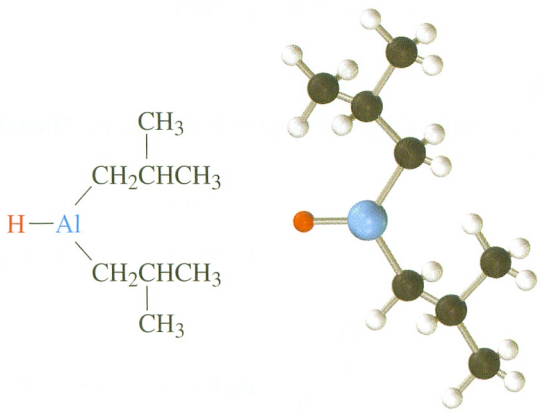
Lithium tri-*t*-butoxyaluminum hydride [$LiAlH(Ot\text{-}Bu)_3$]
(reduces an acyl chloride but not an aldehyde)

The steric hindrance caused by the bulky tertiary butoxy groups makes this reagent much less reactive than lithium aluminum hydride. At low temperature (−78°C) it is reactive enough to attack the carbonyl carbon of an acyl chloride, but it reacts only slowly with the aldehyde product. Examples of the use of this reagent to prepare aldehydes are provided in the following equations:



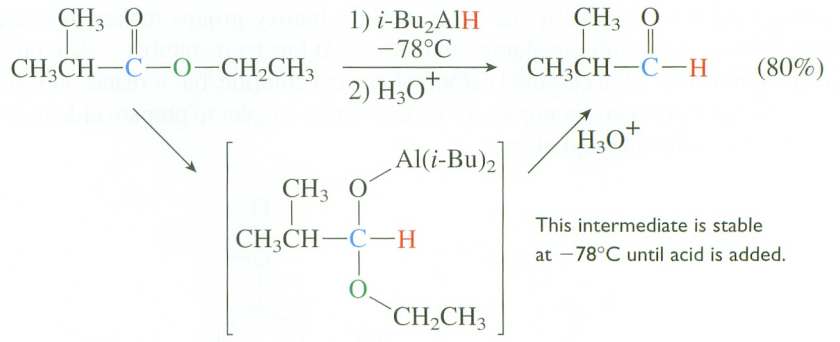


Numerous other metal hydride reagents have been developed to accomplish a variety of specialized reductions. The only other one that will be discussed here is diisobutylaluminum hydride, *i*-Bu_2AlH or DIBALH:



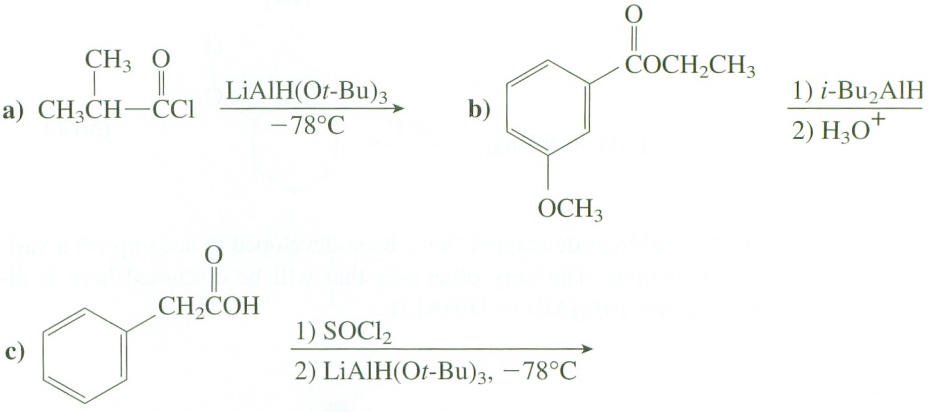
Diisobutylaluminum hydride
(DIBALH or *i*-Bu_2AlH)

This reagent reduces esters to aldehydes at low temperatures. On the basis of the preceding discussion, we might wonder why the aldehyde is not also reduced by this reagent, because it is reactive enough to attack the ester. The reason is that the aldehyde is not produced until acid is added to the reaction mixture during the workup. The initial intermediate, with a diisobutylaluminum group bonded to the oxygen, is stable at low temperature and does not expel ethoxide ion to produce the aldehyde. Therefore, the aldehyde is never in the presence of the reducing agent. The following equation provides an example:



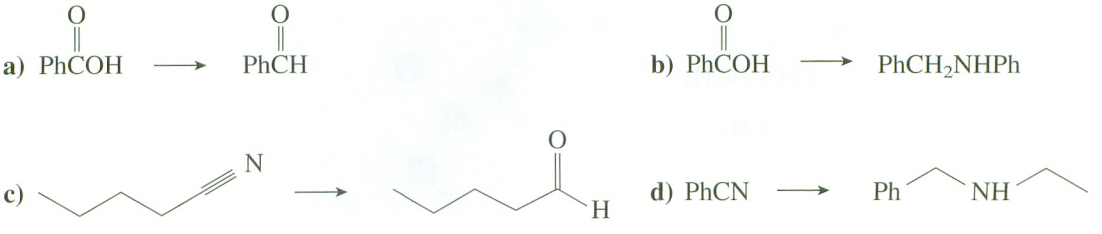
PROBLEM 19.19

Show the products of these reactions:



PROBLEM 19.20

Suggest methods to accomplish the following transformations. More than one step may be necessary in some cases.



19.9 Reactions with Organometallic Nucleophiles

Similar to the case for its reaction with lithium aluminum hydride, an ester reacts with a Grignard or organolithium reagent to produce a ketone as the initial product. But because the ketone also reacts with the organometallic reagent, an alcohol is the final product. The mechanism for this reaction is shown in Figure 19.10. Note the similarities between this mechanism and that shown in Figure 19.7 for the reduction of an ester with lithium aluminum hydride.

❶ The organometallic nucleophile attacks the carbonyl carbon and displaces the pi electrons onto the oxygen.

❷ The electrons on the negative oxygen reform the pi bond as the ethoxide anion leaves.

❸ The ketone also reacts with the Grignard reagent as discussed in Chapter 18.

❹ When the reaction is worked up by the addition of acid, the alkoxide ion is protonated to produce an alcohol. In this example the yield is 67%.

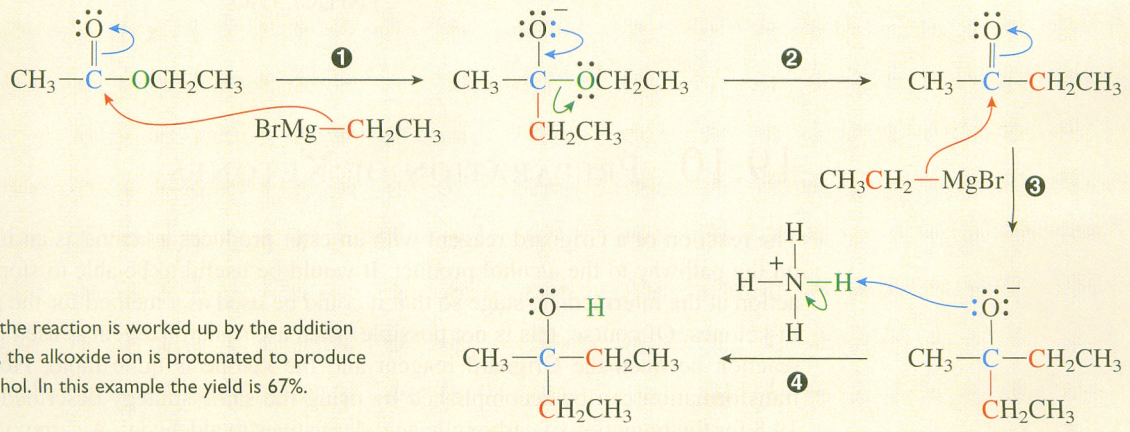
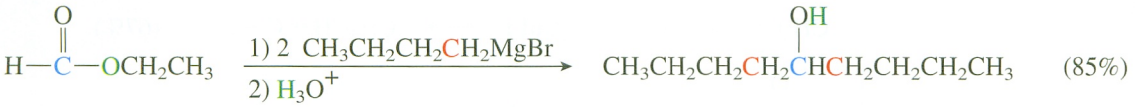
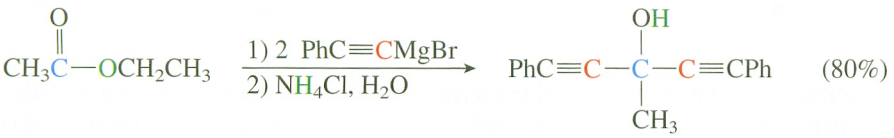


Figure 19.10

MECHANISM OF THE REACTION OF A GRIGNARD REAGENT WITH AN ESTER.

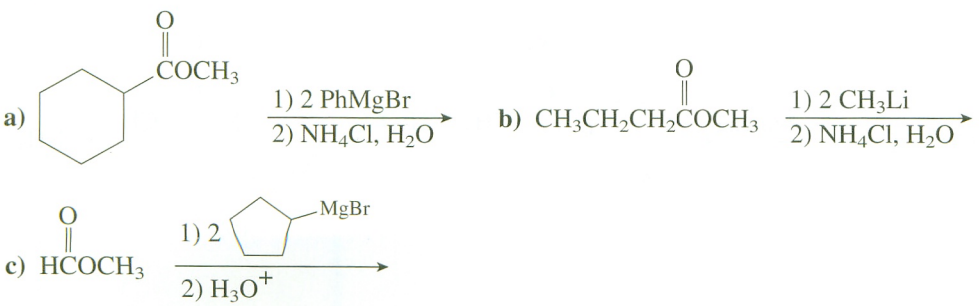
This reaction is a useful method to prepare alcohols with two identical groups on the carbon bonded to the hydroxy group. Formate esters produce secondary alcohols; other esters produce tertiary alcohols. Examples are provided in the following equations. Again, acyl chlorides and anhydrides also give this reaction, but they are seldom used because they offer no advantages over esters.





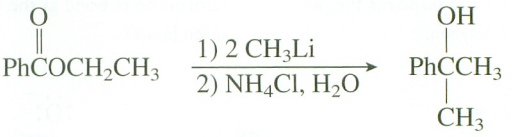
PROBLEM 19.21

Show the products of these reactions:



PROBLEM 19.22

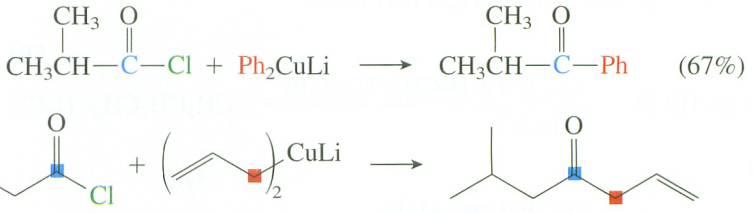
Show all of the steps in the mechanism for this reaction:



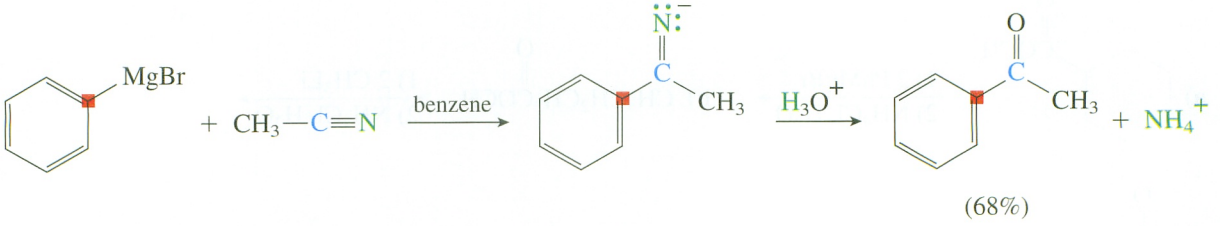
19.10 PREPARATION OF KETONES

The reaction of a Grignard reagent with an ester produces a ketone as an intermediate on the pathway to the alcohol product. It would be useful to be able to stop such a reaction at the intermediate stage so that it could be used as a method for the preparation of ketones. Of course, this is not possible when a Grignard reagent is used because the reaction between the Grignard reagent and the ketone is quite rapid. However, this transformation can be accomplished by using the same strategy described in Section 19.8 for the reduction of carboxylic acid derivatives to aldehydes. A carboxylic acid derivative that is more reactive than a ketone, such as an acyl chloride, and an organometallic nucleophile that will react with the acyl chloride but not the ketone are required.

This transformation can be accomplished by the reaction of a lithium diorganocuprate reagent with an acyl chloride. Recall that this reagent is prepared from the organolithium reagent by reaction with cuprous iodide, CuI (see Section 18.10). Those containing methyl, primary alkyl, aryl, or vinyl groups add to acyl chlorides to give ketones as illustrated in the following examples:

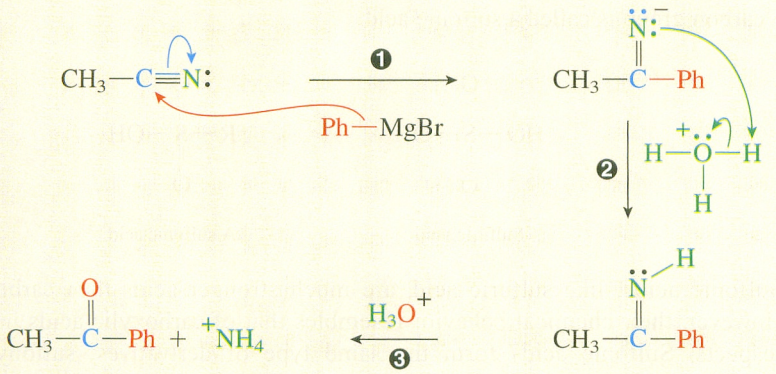


Another method that can be used to prepare ketones is the reaction of a nitrile with a Grignard reagent. In this case the CN double bond of the initial adduct (see Figure 19.11) does not react with the Grignard reagent because the negative charge on the nitrogen makes the carbon too weak as an electrophile. Addition of acid during the workup produces an imine, which is hydrolyzed to a ketone by the reverse of the mechanism shown in Figure 18.3 on page 766. An example is shown in the following equation:



❶ The nucleophile attacks the electrophilic carbon of the cyano group.

This intermediate is too weak an electrophile to react with the Grignard reagent. It is stable in the solution until acid is added during the workup.



❸ The imine is hydrolyzed to a ketone by the reverse of the mechanism shown in Figure 18.3.

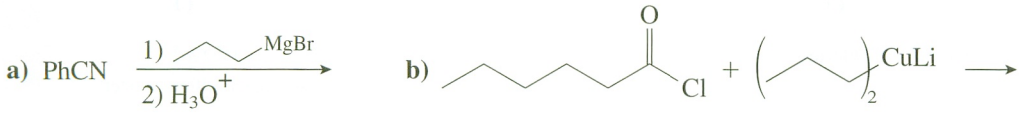
❷ Addition of acid to the reaction solution produces an imine.

Figure 19.11

MECHANISM OF THE REACTION OF A GRIGNARD REAGENT WITH A NITRILE TO PRODUCE A KETONE.

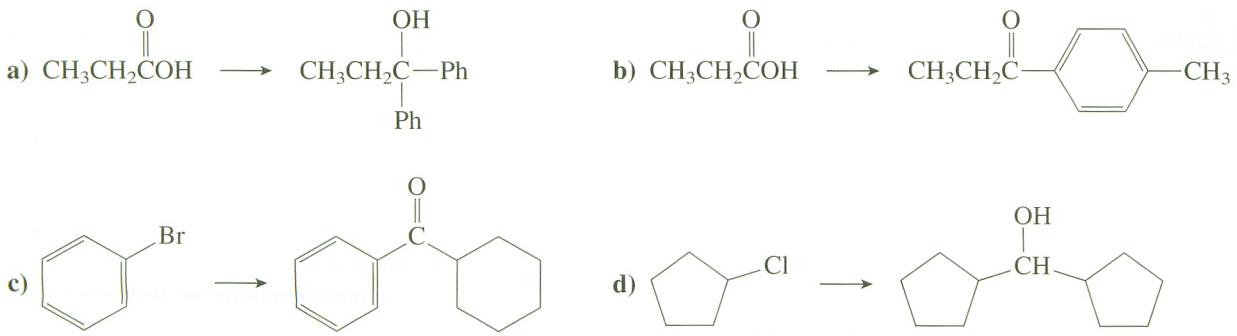
PROBLEM 19.23

Show the products of these reactions:



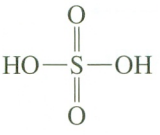
PROBLEM 19.24

Suggest methods to accomplish the following transformations. More than one step may be necessary in some cases.

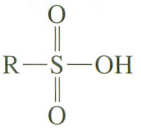


19.11 Derivatives of Sulfur and Phosphorus Acids

A compound in which one of the hydroxy groups of sulfuric acid has been replaced by a carbon group is called a sulfonic acid.



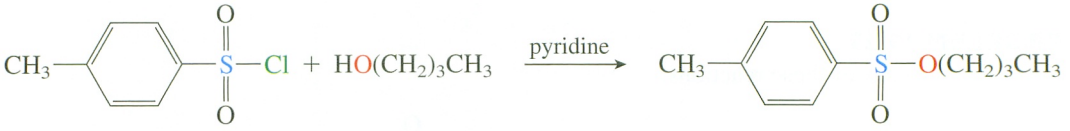
Sulfuric acid



A sulfonic acid

Sulfonic acids, like sulfuric acid, are much stronger acids than carboxylic acids. However, their chemical behavior resembles that of carboxylic acids in many other respects. Sulfonic acids form the same type of derivatives, sulfonyl chlorides, esters, amides, and so on, as do carboxylic acids. These derivatives are interconverted by nucleophilic substitution reactions that resemble those of carboxylic acid derivatives.

The preparation of tosylate and other sulfonate esters for use as leaving groups in nucleophilic substitution reactions (see Section 8.9) employs the reaction of a sulfonyl chloride (an acid chloride of a sulfonic acid) with an alcohol. Another example is shown in the following equation. Note the similarity of this reaction to the reaction of an acyl chloride with an alcohol to form an ester.

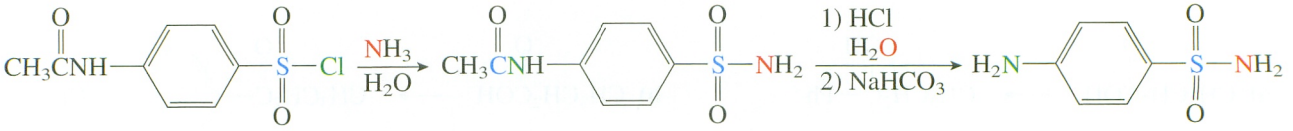


p-Toluenesulfonyl chloride

(90%)

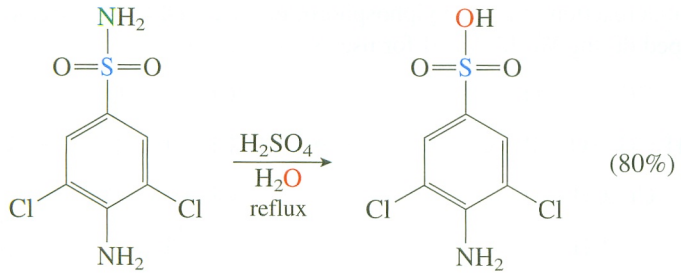
A toluenesulfonate ester

As expected, the reaction of a sulfonyl chloride with ammonia produces a sulfonamide. This reaction is used in the preparation of sulfanilamide, a sulfa drug that was one of the first antibacterial agents:



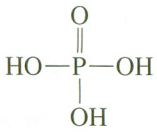
p-Aminobenzenesulfonamide (sulfanilamide)

In the second step of this process, the carboxylic acid amide is hydrolyzed without cleaving the sulfonamide group, illustrating the lower reactivity of the latter. However, sulfonamides can be hydrolyzed by using more vigorous conditions, as illustrated in the following example:

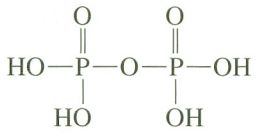


(80%)

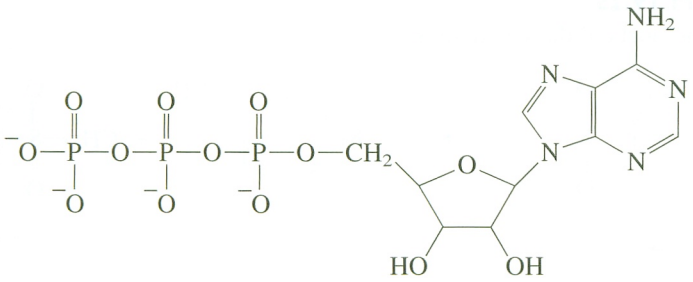
Derivatives of phosphoric acid, pyrophosphoric acid, and related compounds are very important in biological systems. Pyrophosphoric acid is an anhydride of phosphoric acid. Adenosine triphosphate, an energy carrier that is universally found in living organisms, has a phosphorus dianhydride connected to an adenosine group by a phosphate ester linkage. Phosphorus ester bonds are used to form the polymeric backbone of DNA (see Chapter 27).



Phosphoric acid

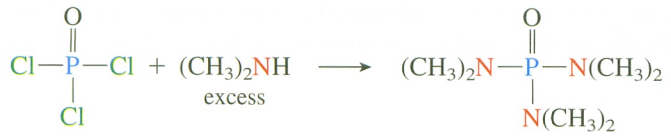


Pyrophosphoric acid



Adenosine triphosphate
(ATP)

Although phosphoric acid has three hydroxy groups that can be used to form derivatives, the various reactions involved are again similar to those of carboxylic acids. For example, the reaction of phosphorus oxychloride, which can be viewed as a tri(acid chloride) of phosphoric acid, with excess dimethyl amine produces a triamide, hexamethylphosphoric triamide:

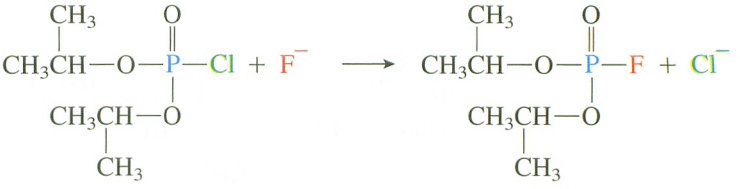


Phosphorus
oxychloride

Hexamethylphosphoric triamide
(HMPA)

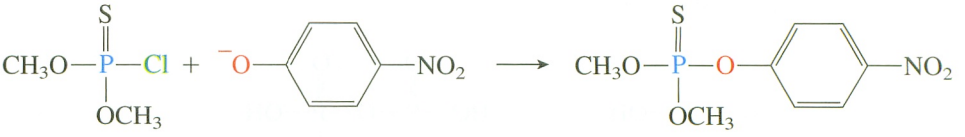
In the reaction illustrated in the following equation, a fluoride nucleophile replaces the chlorine of a derivative that can be viewed as both a diester and an acid chloride. The

product of this reaction, diisopropylphosphorofluoridate (DFP), is extremely toxic and was developed during World War II for use as a nerve gas.



Diisopropylphosphorofluoridate (DFP)

Methyl parathion, an insecticide, is prepared by a similar reaction. The change to a phosphorus–sulfur double bond, rather than a phosphorus–oxygen double bond, does not have a dramatic effect on the chemistry of the compound.



Methyl parathion

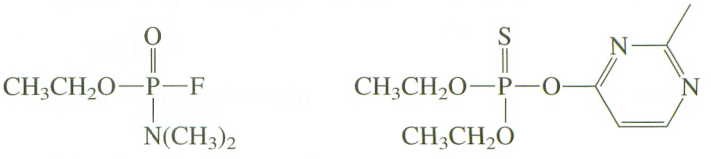
PROBLEM 19.25

Show the products of these reactions:

Focus On Biological Chemistry

Nerve Gases and Pesticides

Nerve gases, such as DFP and tabun, and pesticides, such as methyl parathion and diazinon, generally exhibit their toxic effect by interfering with the transmission of nerve signals.



Tabun

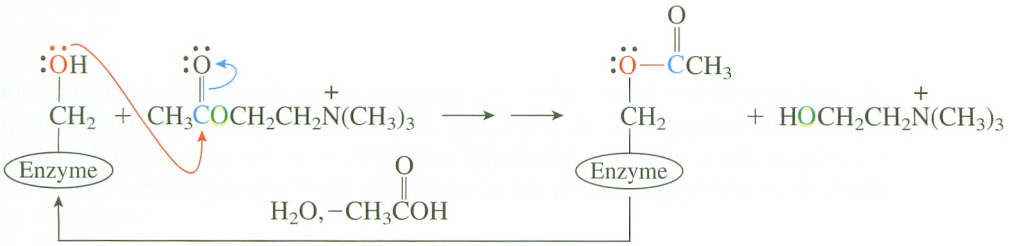
Diazinon

The signals between nerve cells are transmitted by chemicals known as neurotransmitters. Acetylcholine is an important neurotransmitter that is involved in the sig-

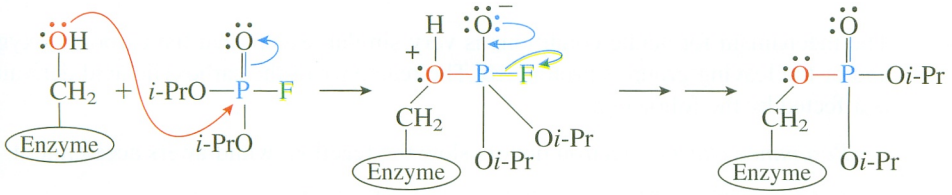
nal from nerves to muscles. The nerve releases acetylcholine, which binds to receptors on the muscle cell, causing it to contract. An enzyme, acetylcholinesterase, catalyzes the hydrolysis of acetylcholine, decomposing it so that the muscle can relax until another contraction is caused by another release of acetylcholine from the nerve cell. If the acetylcholine is not hydrolyzed, the muscle is paralyzed.

Acetylcholine Choline

The mechanism for the hydrolysis that is catalyzed by the enzyme involves the hydroxy group of a serine amino acid residue in the protein acting as a nucleophile and attacking the carbonyl carbon of the acetylcholine ester. The ester is cleaved, and the acetyl group becomes bonded to the enzyme. Then the acetyl group is hydrolyzed off the enzyme, enabling it to perform another catalytic cycle. This hydrolysis is very facile, so a single enzyme molecule can catalyze the hydrolysis of many acetylcholine molecules:



The phosphorus-based nerve gases and insecticides act by deactivating acetylcholinesterase. Note that all of these compounds have a good leaving group on the phosphorus. They react readily with the nucleophilic hydroxy group of the enzyme to form a phosphate triester in a reaction that is very similar, both in its mechanism and its product, to the reaction of an acyl chloride with an alcohol to form an ester:



A phosphate triester

Unlike the acetate ester, the phosphate ester is not readily hydrolyzed off the enzyme. Therefore, the enzyme can no longer catalyze the hydrolysis of acetylcholine, and the muscle remains paralyzed. Paralysis of the muscles that are involved in breathing results quickly in asphyxiation and death.

Although there is considerable similarity among the structures of the nerve gases and the pesticides, their toxicity to insects and warm-blooded animals is often quite different. Pesticides that have found commercial applications are much less toxic to humans than are nerve gases. Nevertheless, they are toxic to some extent and must be used with caution. Chemists are continually seeking the perfect pesticide that is very toxic to insects (ideally to a single species of insect) yet completely harmless to higher organisms.

ORGANIC Chemistry Now™
Click *Mastery Goal Quiz* to test how well you have met these goals.

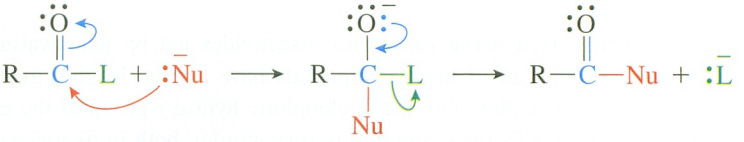
Review of Mastery Goals

After completing this chapter, you should be able to:

- Show the products of any of the reactions discussed in this chapter. (Problems 19.26, 19.27, 19.28, 19.29, 19.33, 19.34, 19.35, 19.36, and 19.49)
- Show the mechanisms for these reactions. (Problems 19.37, 19.41, 19.42, 19.43, 19.44, 19.45, 19.50, 19.55, and 19.56)
- Predict the effect of a change in structure on the rate and equilibrium of a reaction. (Problems 19.30, 19.31, 19.40, 19.47, 19.54, 19.59, and 19.65)
- Use these reactions to interconvert any of the carboxylic acid derivatives and to prepare aldehydes, ketones, alcohols, and amines. (Problems 19.32 and 19.46)
- Use these reactions in combination with reactions from previous chapters to synthesize compounds. (Problems 19.38 and 19.39)

Visual Summary of Key Reactions

The reactions in this chapter follow the same general mechanism. First, the nucleophile bonds to the carbonyl carbon, displacing the pi electrons of the CO double bond onto the oxygen and forming the tetrahedral intermediate. In the second step the unshared electrons on the oxygen reform the pi bond as the leaving group leaves:



Tetrahedral intermediate

The mechanism for acidic conditions is very similar, except that the carbonyl oxygen and/or the leaving group is protonated. The reactivity of the carboxylic acid derivative is affected by the following:

Resonance effects: Electron donors slow the reaction; withdrawers accelerate it.

Inductive effects: Electron withdrawers accelerate the reaction.

Steric effects: Steric hindrance slows the approach of the nucleophile.

The overall reactivity order for the carboxylic acid derivatives (see Table 19.1) is as follows:

Most reactive Least reactive

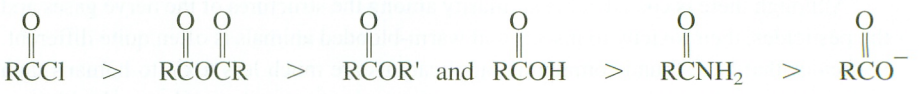
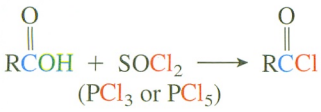
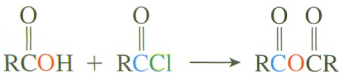
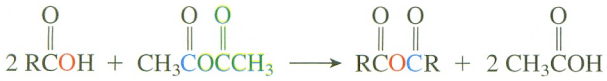
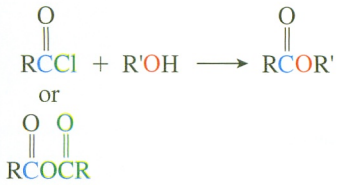
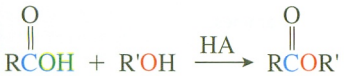
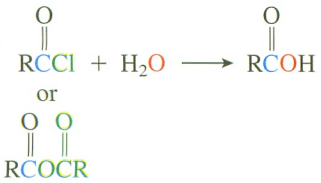
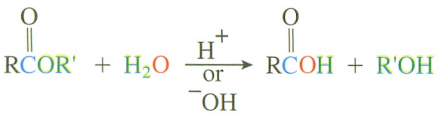
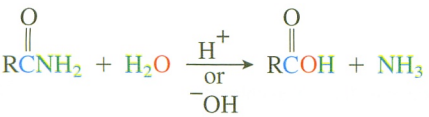
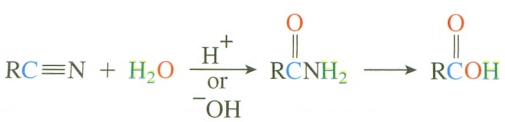


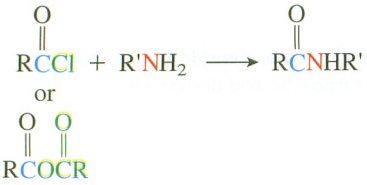
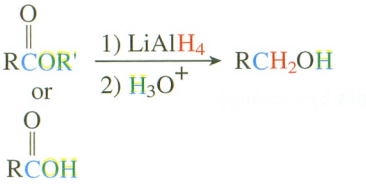
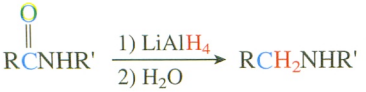
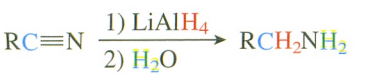
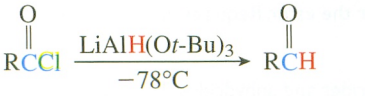
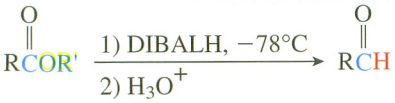
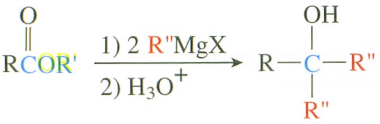
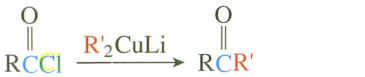
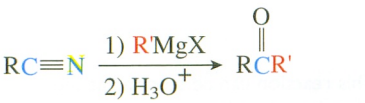
Table 19.2 provides a summary of the reactions presented in this chapter.

Table 19.2 Nucleophilic Substitution Reactions at Carbonyl Carbons

Reaction	Comment
	**Section 19.2** Preparation of acyl chlorides. Acyl chlorides are commonly used to prepare other carboxylic acid derivatives.
	**Section 19.3** Preparation of anhydrides.
	**Section 19.3** Preparation of anhydrides by exchange.
	**Section 19.4** Preparation of esters.
	**Section 19.4** Preparation of esters by Fischer esterification. The equilibrium must be driven to favor the ester. Requires an acid catalyst.
	**Section 19.5** Hydrolysis of acyl chlorides and anhydrides. These derivatives must be protected from water to avoid these reactions.
	**Section 19.5** Hydrolysis of esters. Base is most commonly used in the process known as saponification.
	**Section 19.5** Hydrolysis of amides. This reaction can be accomplished by using either acid or base.
	**Section 19.5** Hydrolysis of nitriles. This reaction can be stopped at the amide or carried to the carboxylic acid.
	The preparation of nitriles by S_N2 reactions combined with hydrolysis of nitriles provides a carboxylic acid preparation.

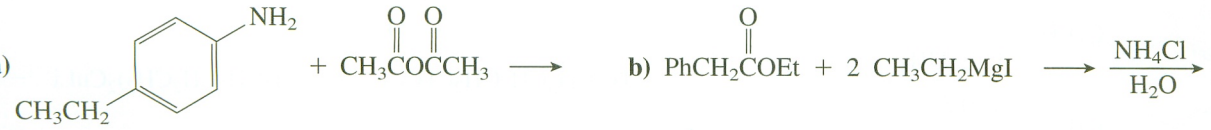
Continued

Table 19.2 Nucleophilic Substitution Reactions at Carbonyl Carbons—cont'd

Reaction	Comment
	**Section 19.6** Preparation of amides.
	**Section 19.7** Reduction of esters or acids to alcohols.
	**Section 19.7** Reduction of amides to amines.
	**Section 19.8** Reduction of nitriles to primary amines.
	**Section 19.8** Reduction of acyl chlorides to aldehydes.
	**Section 19.8** Reduction of esters to aldehydes.
	**Section 19.9** Preparation of alcohols from esters.
	**Section 19.10** Preparation of ketones from acyl chlorides.
	**Section 19.10** Preparation of ketones from nitriles.

Integrated Practice Problem

Show the products of these reactions:



Strategy

A lot of reactions were presented in this chapter. Remember to identify the electrophile (usually the carbonyl carbon of a carboxylic acid derivative) and the nucleophile. The nucleophile bonds to the carbonyl carbon to form the tetrahedral intermediate. Then the leaving group departs as the CO double bond reforms. The product may be subject to further nucleophilic attack.

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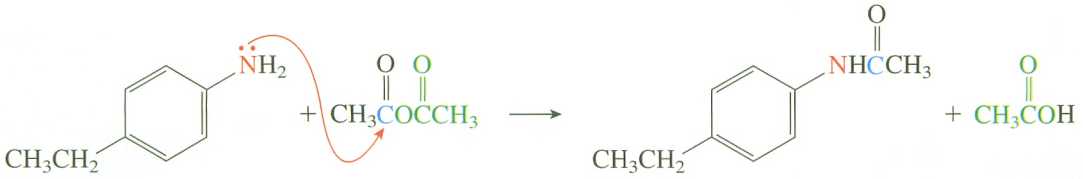
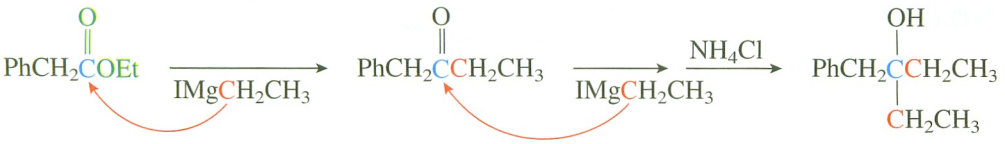
Solutions

a) The electrophile is the carbonyl carbon of the anhydride; the nucleophile is the nitrogen of the aromatic amine. The nitrogen replaces the acetate group, so the ultimate products are an amide and acetic acid.



b) The electrophile is the carbonyl carbon of the ester. The nucleophile is the carbon bonded to the magnesium of the Grignard reagent. In the first part of the reaction, the nucleophile bonds to the carbonyl carbon, replacing the EtO^- group. The product of this step is a ketone, which still has an electrophilic carbonyl carbon that reacts with the second Grignard reagent. The final product is a tertiary alcohol with two ethyl groups bonded to the original carbonyl carbon of the ester group.



Additional Problems

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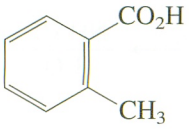
Assess your understanding of this chapter's topics with additional quizzing and conceptual-based problems at **http://now.brookscole.com/hornback2**

PROBLEM 19.26

Show the products of these reactions:

c) $PhCH_2COH \xrightarrow{SOCl_2} PhCH_2CO^- \longrightarrow$

d) $PhCO_2H + CH_3CH_2CH_2CH_2OH \xrightarrow{H_2SO_4}$

e)  $\xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4}$

f) $CH_3CH_2CH_2CH_2CCl + (CH_3CH_2CH_2CH_2)_2CuLi \longrightarrow$

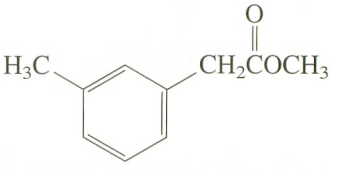
g) $CH_3CH_2CH_2C{\equiv}N \xrightarrow[2)\ H_2O]{1)\ LiAlH_4}$

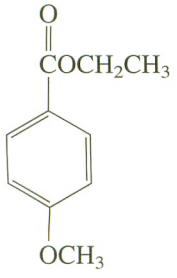
h) $CH_2{=}CHCCl + CH_3CH_2OH \longrightarrow$

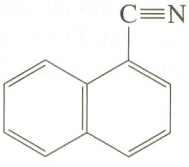
i) $CH_3CH(CH_3)CO_2H \xrightarrow{SOCl_2} \xrightarrow[H_2O]{NH_3}$

j) $CH_3(CH_2)_{10}CH_2OH + ClSO_2C_6H_4CH_3 \xrightarrow{pyridine}$

k) $NCCH_2CH_2CH_2CN \xrightarrow[H_2O]{HCl}_{\Delta}$

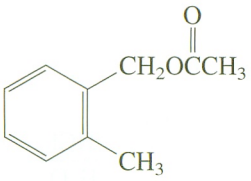
l)  $\xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4}$

m)  $\xrightarrow[2)\ H_3O^+]{1)\ DIBALH,\ -78°C}$

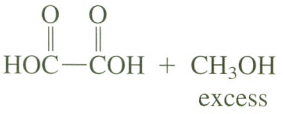
n)  $\xrightarrow{CH_3MgI} \xrightarrow{H_3O^+}$

o) $PhCH(OH)CPh{=}O + CH_3COCCH_3{=}O \longrightarrow$

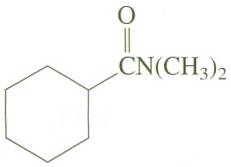
p) $\xrightarrow[H_2O]{HCl}_{\Delta} \xrightarrow{NaOH}$

q) 

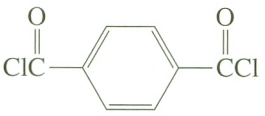
$\xrightarrow[H_2O]{NaOH}$

r) 

$\xrightarrow{H_2SO_4}$

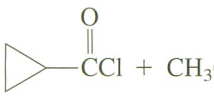
s) 

$\xrightarrow[2)\ H_2O]{1)\ LiAlH_4}$

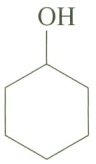
t) 

$\xrightarrow[-78°C]{2\ LiAlH(Ot\text{-}Bu)_3}$

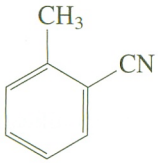
19.27 Show the products of these reactions:

a) 

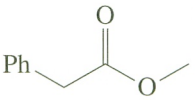
$\longrightarrow$

b) 

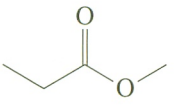
$\xrightarrow{H_2SO_4}$

c) 

$\xrightarrow[H_2SO_4]{H_2O}$ long time

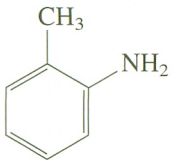
d) 

$\xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4}$

e) 

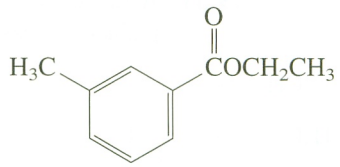
$\xrightarrow[2)\ NH_4Cl,\ H_2O]{1)\ 2}$

19.28 Show the products of these reactions:

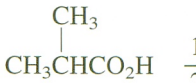
a) 

+

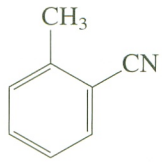
$\longrightarrow$

b) 

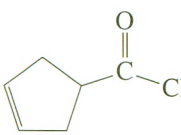
$\xrightarrow[H_2O]{NaOH}$

c) 

$\xrightarrow[2)\ NH_3,\ H_2O]{1)\ SOCl_2}$

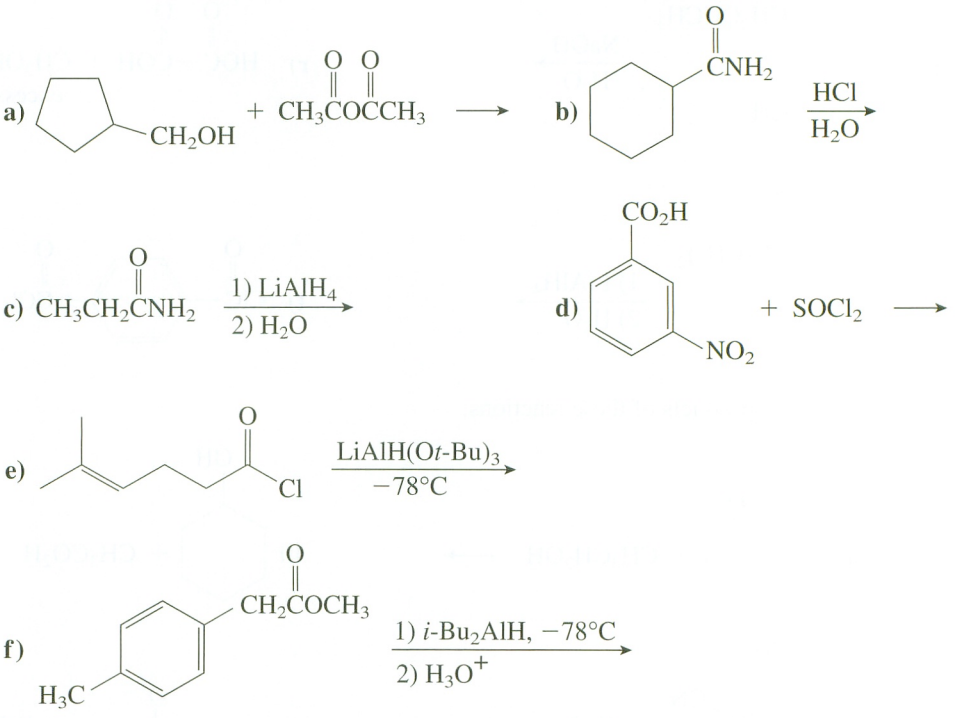
d) 

$\xrightarrow[2)\ H_2O]{1)\ LiAlH_4}$

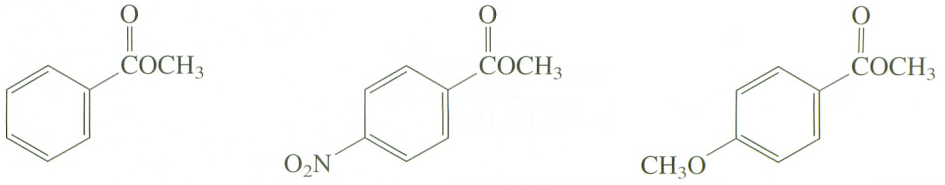
e) 

$\longrightarrow$

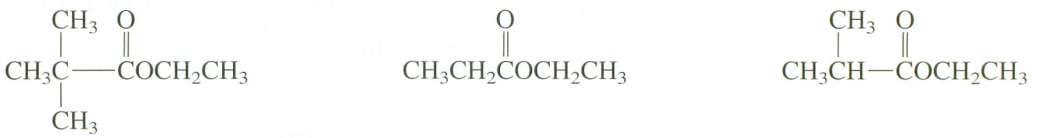
19.29 Show the products of these reactions:



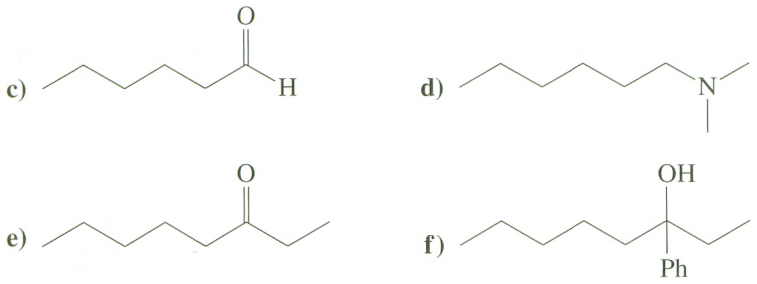
19.30 Arrange these compounds in order of increasing rate of saponification and explain your reasoning:



19.31 Arrange these compounds in order of increasing rate of saponification and explain your reasoning:



19.32 Suggest syntheses of these compounds starting from hexanoic acid:



19.33 Show the products of the reaction of benzoic acid with each of these reagents:

a) 1) $SOCl_2$ 2) CH_3OH **b)** $CH_3\overset{\displaystyle CH_3}{\underset{|}{C}}HOH$, H_2SO_4

c) 1) $LiAlH_4$ 2) H_3O^+ **d)** CH_3NH_2

e) CH_3NH_2, Δ

19.34 Show the products of the reaction of benzoyl chloride with each of these reagents:

a) $PhNH_2$ **b)** $CH_3\overset{\displaystyle OH}{\underset{|}{C}}HCH_3$

c) $PhC(=O)O^-$ **d)** $LiAlH(Ot\text{-}Bu)_3$, $-78°C$

e) H_2O **f)** $(CH_3)_2CuLi$

19.35 Show the products of the reaction of ethyl benzoate with each of these reagents:

a) 1) 2 CH_3CH_2MgBr 2) NH_4Cl, H_2O

b) 1) $i\text{-}Bu_2AlH$, $-78°$ 2) H_3O^+

c) $NaOH$, H_2O

d) 1) $LiAlH_4$ 2) H_3O^+

e) H_3O^+, H_2O

19.36 Show the products of the reaction of *N*-methylbenzamide with each of these reagents:

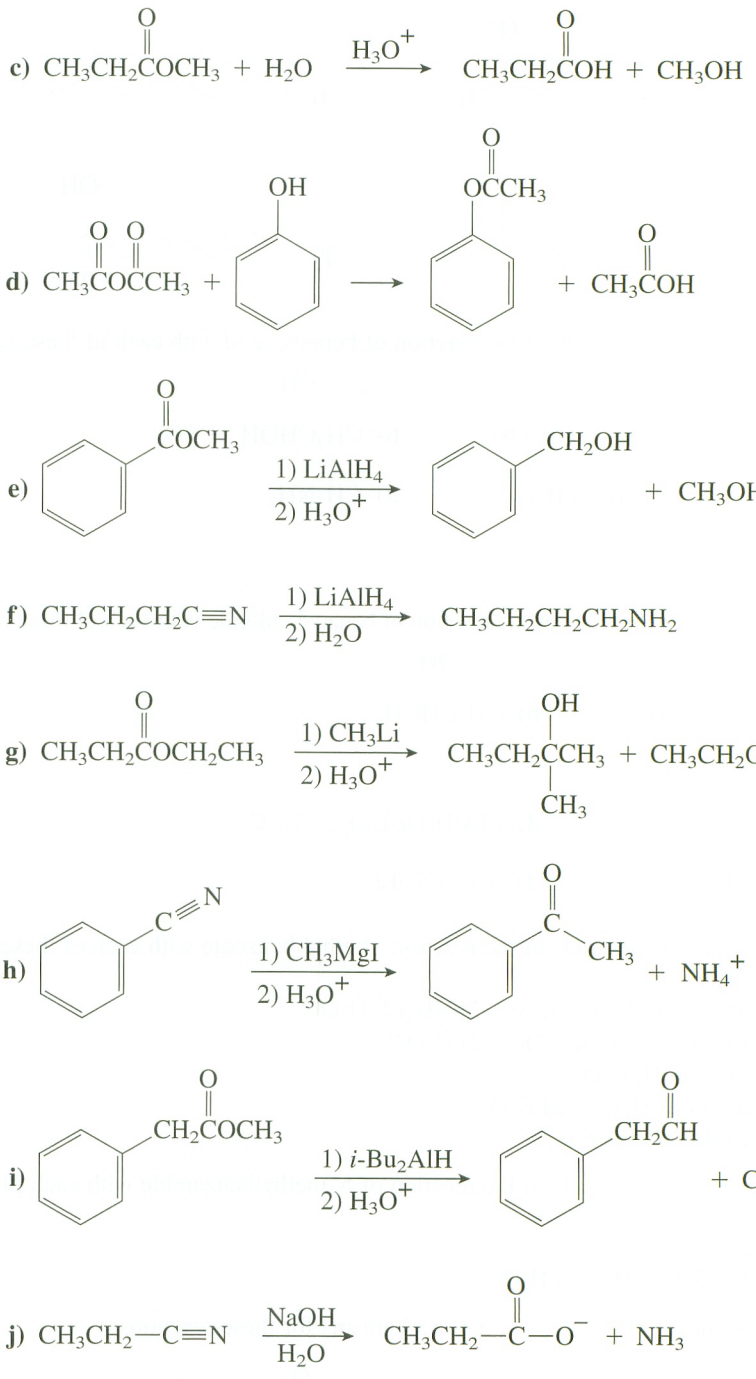
a) HCl, H_2O

b) 1) $LiAlH_4$ 2) H_2O

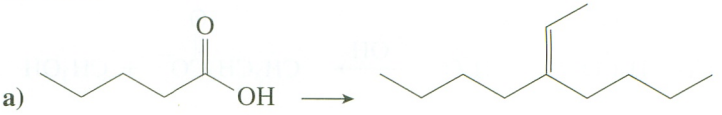
19.37 Show all of the steps in the mechanisms for these reactions:

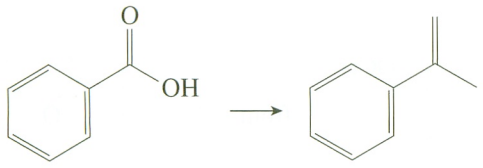
a) $CH_3C{\equiv}N + H_2O \xrightarrow{H_3O^+} CH_3\overset{\displaystyle O}{\underset{\|}{C}}NH_2$

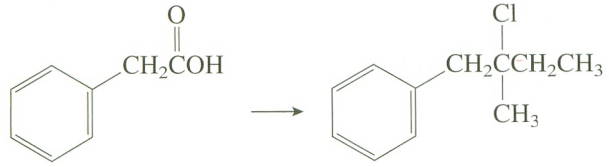
b) $CH_3CH_2\overset{\displaystyle O}{\underset{\|}{C}}OCH_3 + H_2O \xrightarrow{^-OH} CH_3CH_2\overset{\displaystyle O}{\underset{\|}{C}}O^- + CH_3OH$

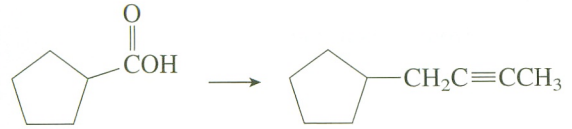


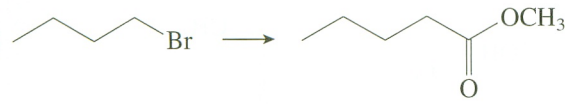
19.38 Show syntheses of these compounds from the indicated starting materials:



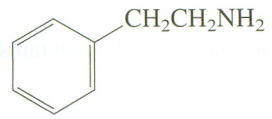
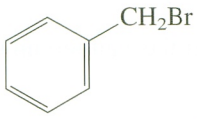
b) 

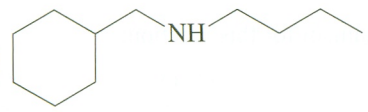
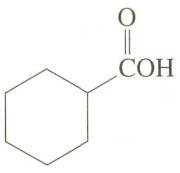
c) 

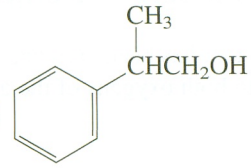
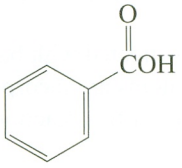
d) 

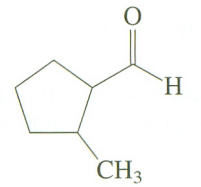
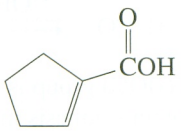
e) 

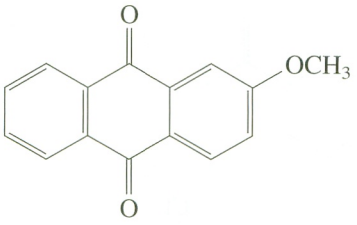
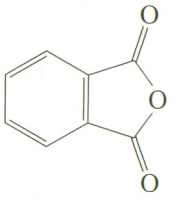
19.39 Show syntheses of these compounds from the indicated starting materials:

a)  from 

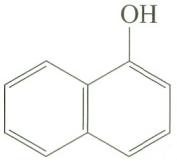
b)  from 

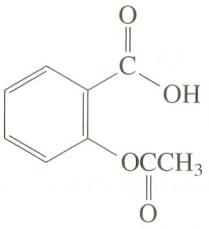
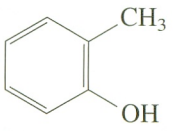
c)  from 

d)  from 

e)  from 

f) Ph_3COH from CH_3I

g)  from benzene

h)  from 

19.40 Explain whether the equilibrium in this reaction favors the reactants or the products:

$$CH_3\overset{\overset{O}{\|}}{C}OCH_3 + {}^{-}O{-}Ph \rightleftharpoons CH_3\overset{\overset{O}{\|}}{C}OPh + {}^{-}O{-}CH_3$$

19.41 Show all of the steps in the mechanism for this reaction:

$$2\ PhCOH + CH_3\overset{\overset{O}{\|}}{C}\overset{\overset{O}{\|}}{C}CH_3 \rightleftharpoons PhCOCPh + 2\ CH_3\overset{\overset{O}{\|}}{C}OH$$

19.42 When acetate ion is treated with basic water that has been enriched with ^{18}O, the heavy oxygen atoms are incorporated into both oxygens of the acetate ion. Show a mechanism for this reaction.

$$CH_3\overset{\overset{O}{\|}}{C}{-}O^{-} + H_2{}^{18}O \xrightleftharpoons{{}^{18}OH^{-}} CH_3\overset{\overset{{}^{18}O}{\|}}{C}{-}{}^{18}O^{-} + H_2O$$

BioLink

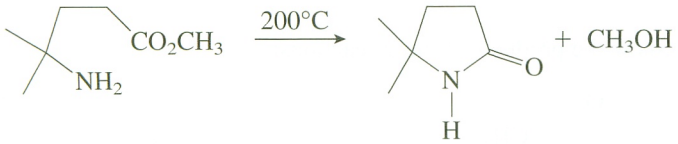
19.43 The *tert*-butoxycarbonyl (BOC) group is used to protect the amino group of an amino acid during protein synthesis in the laboratory. The BOC group is attached to the amine by this reaction:

$$t\text{-BuO}\overset{\overset{O}{\|}}{C}\overset{\overset{O}{\|}}{C}Ot\text{-Bu} + NH_2{-}R \longrightarrow t\text{-BuO}\overset{\overset{O}{\|}}{C}NH{-}R + \left[HO\overset{\overset{O}{\|}}{C}Ot\text{-Bu}\right]$$

Show the steps in the mechanism for this reaction and explain why the following product is not formed:

Not formed

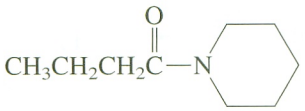
19.44 Show the steps in the mechanism for this reaction:



19.45 Esters are occasionally prepared by an interchange reaction as shown in this equation:

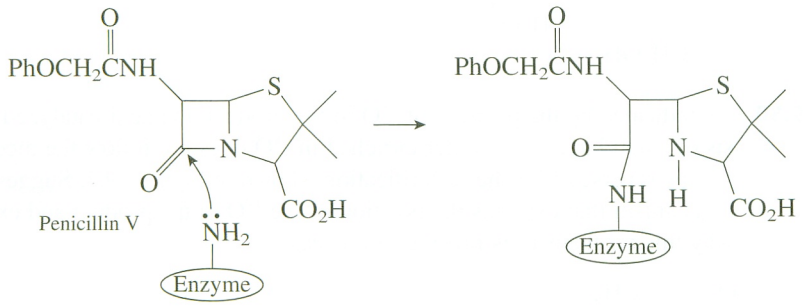
a) Show the steps in the mechanism for this reaction.
b) What is the approximate equilibrium constant for this reaction?
c) How could the equilibrium be driven toward the products?

19.46 Amides are occasionally prepared by the reaction of an amine with an ester. Show how this amide could be prepared by this procedure. Is it necessary to drive the equilibrium toward the products in this case?

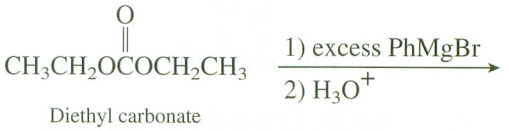


19.47 Penicillins have a four-membered lactam ring. These antibiotics apparently work by reacting with an NH_2 nucleophile at the active site of an enzyme that is important in the bacterium, as shown in the following equation. What makes the equilibrium favorable for this reaction?

BioLink

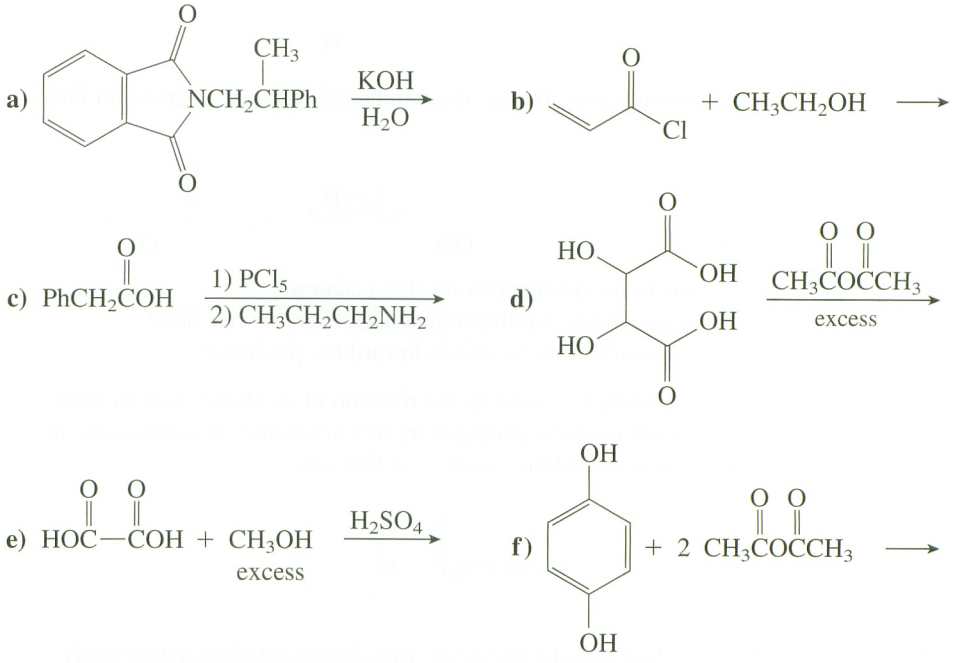


19.48 Grignard reagents react with carbonate esters in a similar manner to their reactions with other esters. Predict the products of this reaction:

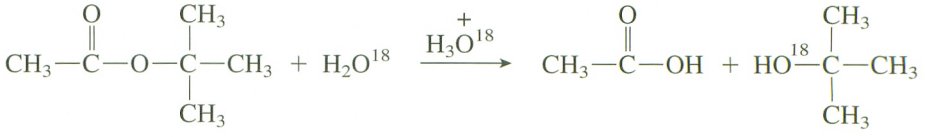


Diethyl carbonate
(a carbonate ester)

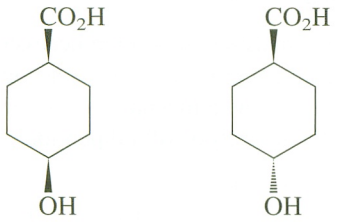
19.49 Show the products of these reactions:



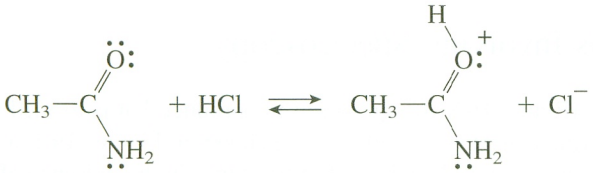
19.50 As indicated by the position of ^{18}O in the product, the acid-catalyzed hydrolysis of *t*-butyl acetate in water enriched in ^{18}O does not follow the mechanism for the reverse of Fischer esterification, shown in Figure 19.3. Suggest a mechanism that explains the position of the ^{18}O in the product and explain why this mechanism is favored in this case.



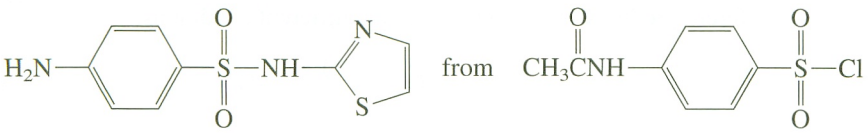
19.51 Explain why one of these compounds forms a lactone when heated and the other does not. Show the structure of the lactone.



19.52 Even though nitrogen is usually more basic than oxygen, when an amide is protonated the proton becomes bonded to the oxygen. Explain this observation.



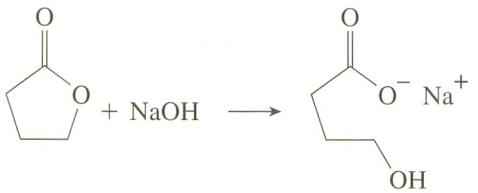
19.53 Suggest a synthesis of sulfathiazole, a sulfa drug, from the indicated starting material:



Sulfathiazole

19.54 The hydrolysis shown in the following equation occurs readily in cold water. Explain why this reaction is so much faster than the hydrolysis of an amide, which requires heat and the presence of acid or base.

19.55 Sodium 4-hydroxybutanoate, also known as gamma hydroxybutyrate (GHB) and liquid ecstacy, is an illegal drug that produces a euphoric effect similar to drunkenness. Overdoses can cause vomiting, muscle spasms, and unconsciousness. Because of its knockout capability, it is associated with sexual assaults and date rape. GHB can be prepared from gamma butyrolactone (GBL) by reaction with sodium hydroxide as shown in the following equation:

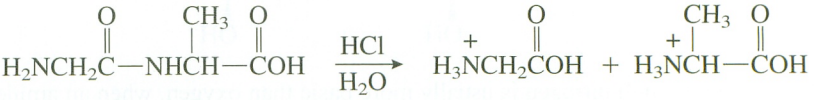


GBL GHB

Show a mechanism for the conversion of GBL to GHB. Explain why the equilibrium favors GHB in this reaction. Explain why GHB is converted back to GBL when treated with acid.

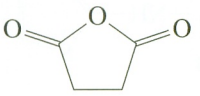
BioLink

19.56 When proteins are analyzed, it is often necessary to cleave them into their individual amino acid components. This is accomplished by refluxing the protein in acidic water. Show a mechanism for this process using the following model reaction, the hydrolysis of a dipeptide:



Problems Involving Spectroscopy

19.57 The IR and ^{1}H-NMR spectra of the product that is formed when succinic anhydride is heated in methanol are shown in Figures 19.12a and 19.12b. When succinic anhydride is heated in methanol in the presence of a catalytic amount of sulfuric acid, the product with the IR spectrum shown in Figure 19.12c is formed instead. This compound shows only three absorptions in its ^{13}C-NMR spectrum. Show the structures of both of these products and explain why different products are formed under the different conditions.



Succinic anhydride

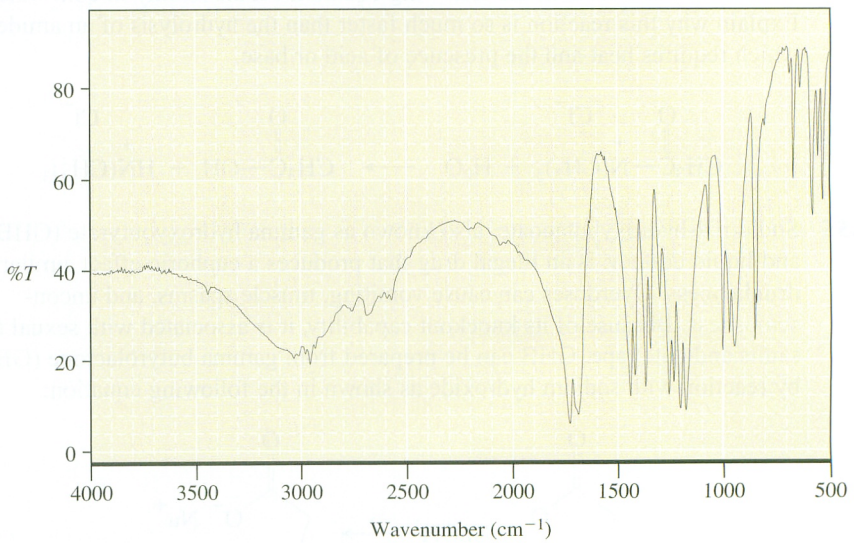


Figure 19.12a

SPECTRA TO ACCOMPANY PROBLEM 19.57.

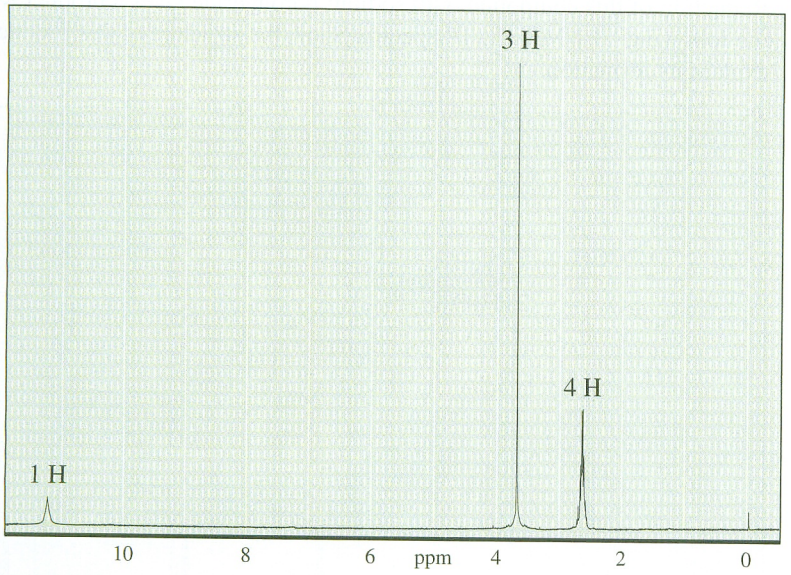


Figure 19.12b

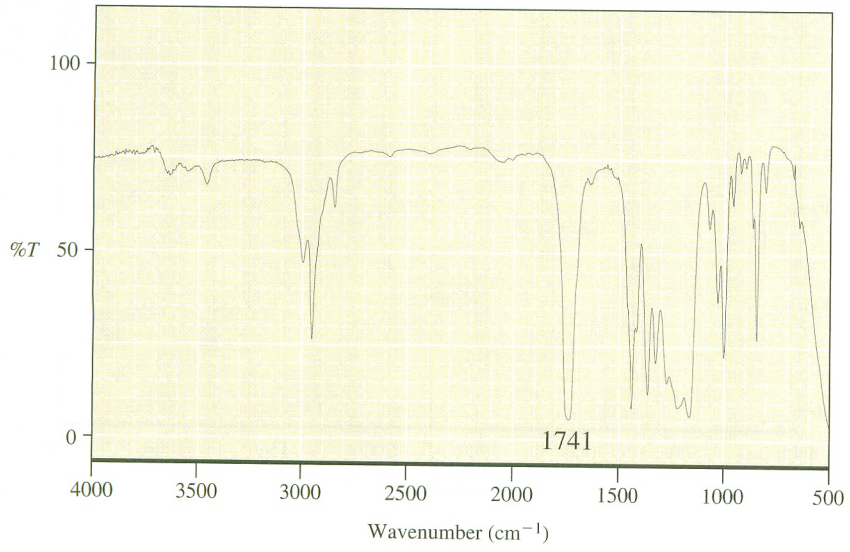
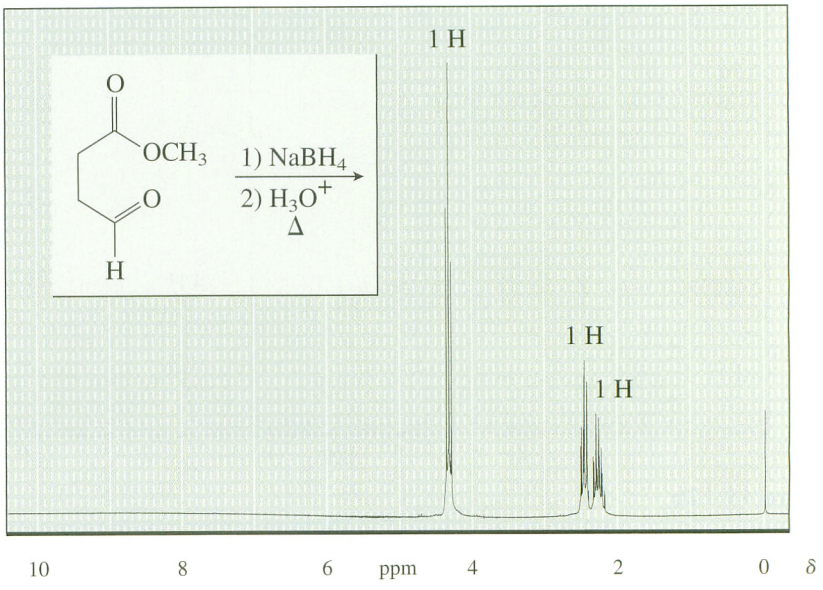
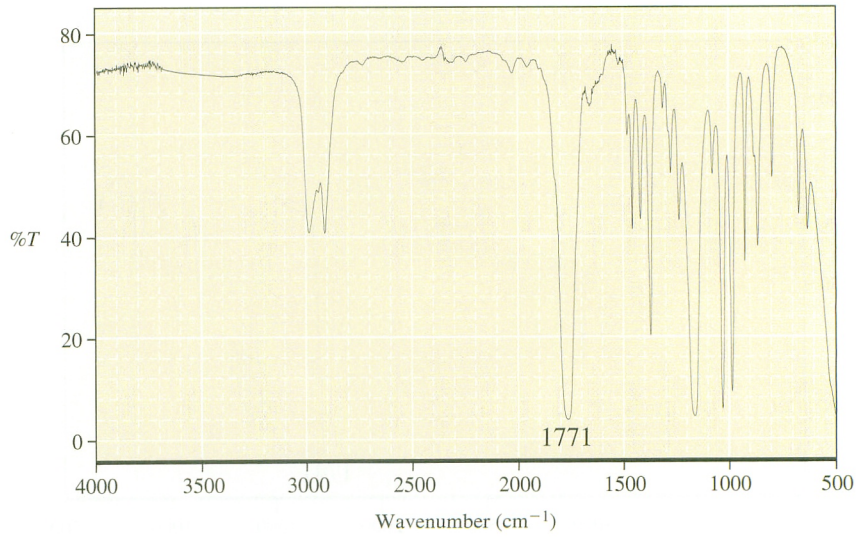


Figure 19.12c

19.58 Reduction of this compound with sodium borohydride gives a product with the following ^{1}H-NMR and IR spectra. Show the structure of this product and explain its formation.





Problems Using Online Three-Dimensional Molecular Models

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19.59 Arrange these carboxylic acids in order of increasing rate of reaction with ethanol and acid to form their ethyl esters and explain your reasoning.

19.60 This methyl ester is very resistant to saponification under conditions where most esters react rapidly. Explain this observation.

19.61 These four stereoisomers contain both a carboxylic acid group and a hydroxy group. Explain which isomers can form a lactone and which cannot.

19.62 Fatty acids (the carboxylic acids produced by saponification of fats) usually have an even number of carbons and may also have one or more cis double bonds. The fatty acid that has 18 carbons with a cis double bond at the 9 position, (*Z*)-9-octadecenoic acid, is called oleic acid. Catalytic hydrogenation of oleic acid produces stearic acid, or octadecanoic acid, another fatty acid. One of these fatty acids melts at 13.4°C and the other melts at 69.6°C. Explain which fatty acid melts at the higher temperature.

19.63 When treated with HCl, one of these isomeric carboxylate anions forms a compound with a pK_a of about 5. The other carboxylate anion forms a compound that has no proton with a pK_a of less than 20. Explain these results.

19.64 One of these stereoisomeric hydroxy acids readily forms a lactone upon heating, whereas the other does not. Explain these results.

19.65 The *trans*-stereoisomer of the ester shown undergoes saponification about 20 times faster than the *cis*-stereoisomer. Explain this observation.

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